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Volume 246 APRIL 10, 1952 Number 15

PREVENTIVE MEDICINE IN OBSTETRICS*

DUGALD BAIRD, M.D., F.R.C.O.G.†

ABERDEEN, SCOTLAND

JOHN CLARENCE CUTTER, as has previously been mentioned, was born in 1851 and graduated at Harvard Medical School in 1877, after which he went to Japan as professor of physiology and comparative anatomy in the College of Agriculture in Saffara. Possibly the experience gained in the nine years he held this post strengthened his great belief in the part that preventive medicine might play in influencing the destiny of man. In his will he allocated half of the net income of his estate to the founding of an annual course of lectures on preventive medicine. I am proud to be, in this, the centenary year, the first obstetrician chosen to deliver a Cutter Lecture.

I propose to deal in this lecture with some of the environmental factors that affect the outcome of pregnancy, rather than with the effects of medical care and treatment during pregnancy or labor.

Reproduction is influenced by heredity and environment. The importance of heredity as a factor in reproduction is proverbial: "like father, like son"; "you cannot make a silk purse out of a sow's ear." There are fewer clichés about the effect of environment, although there is no doubt that reproduction is greatly influenced by custom, tradition, nutrition, standard of education and economic factors.

It seems reasonable to suppose that those who enjoy a high standard of living, — that is to say, good food, housing and education, — will show a higher standard of reproductive performance than those with a low standard of living. The Registrar General's reports in Britain provide a convenient starting-off place for studying death rates by standard of living. He has divided the population into five social classes. Social Class I comprises the more highly paid professional and business groups and Social Class V the casual and unskilled manual laborers. About 50 per cent of the population are in Social Class III, which includes the skilled craftsmen and lower-salaried professional and clerical groups. The classification depends on the social prestige of the occupation as well as on the rate of pay. Analysis of national figures shows that from Social Class I to V there is a steady decline in the stillbirth and infant mortality rates. The influence of social gradient is least in the case of stillbirths and most in the period from one to twelve months. Deaths in the latter group are nearly all due to infection, and the mortality in this period has now been recognized as a very delicate index of environmental conditions. Any deterioration in living standards is reflected immediately in a rise in mortality in the period of one to twelve months. The relatively small difference in the stillbirth rate between the social classes might suggest that superior environment of those in Social Class I did not have much influence in improving reproductive performance. I should like to examine this problem more closely by describing some of the results of our own work on this subject.

The City of Aberdeen is particularly suitable for social research in obstetrics, since there are about 3000 births per annum, a convenient number to handle. The population is genetically fairly uniform; very little movement in and out of the city occurs; and there is only one hospital group. We have studied primigravidas in the first place; 95 per cent of patients having a first baby are confined in hospital, 85 per cent being free (hospital) patients and 10 per cent private (nursing home) patients. The private patients are confined in a former private dwelling house converted for this purpose with a very few minor structural alterations. The total cost to the patient is between £30 and £60.

TABLE 1. *Stillbirth and First-Week Neonatal Death Rates Per 1000 Births in Two Contrasted Groups of Booked Married Primiparas (Twins Excluded).*

	Aberdeen Maternity Hospital 1949–1950 (1792 cases)		Private Nursing Home 1946–1950 (1026 cases)	
	Stillbirth	Non-neonatal Death	Stillbirth	Non-neonatal Death
Full term	10.0	5.6	7.8	8.8
Premature (5½ lb. or less)	12.3	8.9	9.7	1.9
All infants	22.3	14.5	17.5	9.7

*The Cutter Lecture on Preventive Medicine, delivered at Boston, October 15, 1951.

†Regius Professor of Midwifery, University of Aberdeen.

The others are confined in the large teaching hospital and pay no fees. Table 1 shows that both the stillbirth rate and the neonatal mortality are less in the private patients. In the case of neonatal mortality this is due entirely to the very small death rate in premature babies. Table 2 gives a separate analysis of the age group twenty to twenty-four, which emphasizes still further the difference in mortality between these two social groups. The

TABLE 2. *Stillbirth and First-Week Neonatal Death Rates Per 1000 Births Among Booked Primiparas Aged 20 to 24, in 2 Contrasted Groups (Twins Excluded).*

	Stillbirth	Neonatal Death (first week)	Obstetric Death
Aberdeen Maternity Hospital 1949–50 (900 cases)	22.2	16.7	38.9
Private Nursing Home 1946–50 (198 cases)	10.1	5.1	15.2

over-all prematurity rate (babies of five and a half pounds or less) was 5.6 and 8.2 per cent in the private and hospital groups respectively. Figure 1

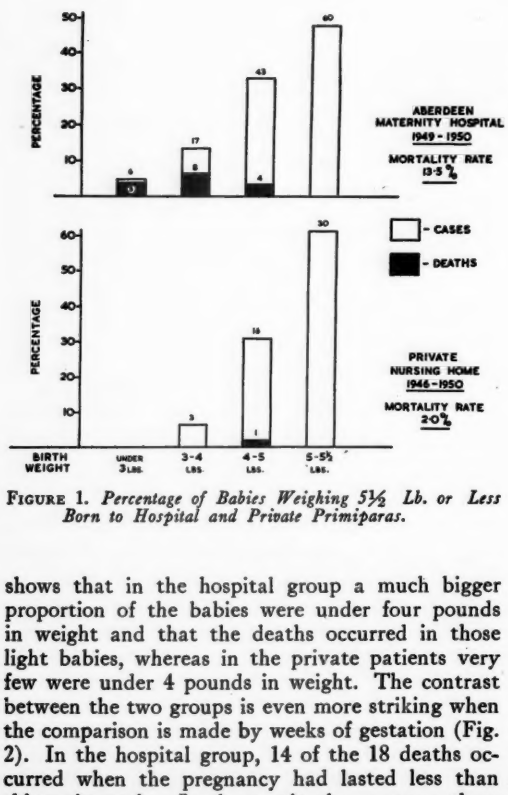

FIGURE 1. *Percentage of Babies Weighing 5½ Lb. or Less Born to Hospital and Private Primiparas.*

shows that in the hospital group a much bigger proportion of the babies were under four pounds in weight and that the deaths occurred in those light babies, whereas in the private patients very few were under 4 pounds in weight. The contrast between the two groups is even more striking when the comparison is made by weeks of gestation (Fig. 2). In the hospital group, 14 of the 18 deaths occurred when the pregnancy had lasted less than thirty-six weeks. In the nursing-home group there was only 1 death among 1043 consecutive premature births. It is clear, therefore, that age for age the primigravidas in private practice are much more efficient, when judged by fetal mortality, than the hospital patients. The relatively small difference in the total stillbirth rate and neonatal mortality is

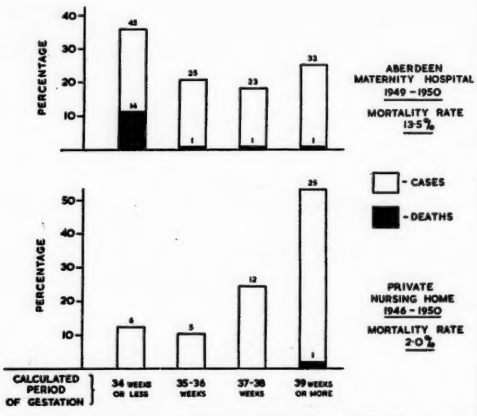

FIGURE 2. *Analysis of Babies Weighing 5½ Lb. or Less Born to Hospital and Private Primiparas, by Gestation Period.*

due to the unfavorable age distribution in the private patients. The difference is not explained by a higher standard of medical care; in fact, the reverse is the case. There are no facilities for the treatment of premature babies in the nursing home,

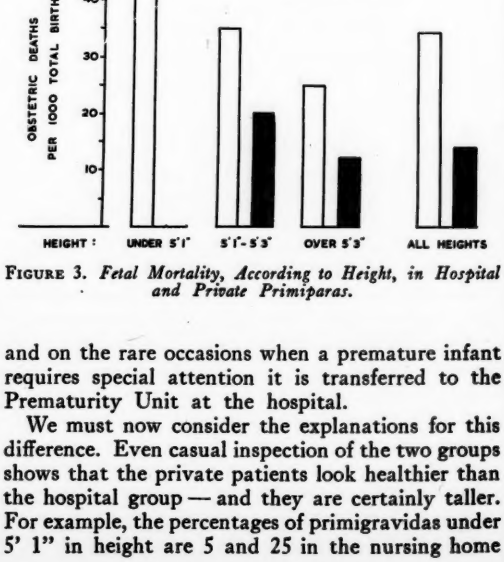

FIGURE 3. *Fetal Mortality, According to Height, in Hospital and Private Primiparas.*

and on the rare occasions when a premature infant requires special attention it is transferred to the Prematurity Unit at the hospital.

We must now consider the explanations for this difference. Even casual inspection of the two groups shows that the private patients look healthier than the hospital group — and they are certainly taller. For example, the percentages of primigravidas under 5' 1" in height are 5 and 25 in the nursing home

and hospital patients respectively. There should, therefore, be a negative correlation between height and high fetal mortality. Figure 3 gives the fetal mortality* by height in primigravidas, and it shows that in both groups the fetal mortality falls as the height of the patient rises. In the private group the fetal mortality in women between twenty and twenty-four years of age and 5 feet 4 inches tall or more reaches the very low figure of 11.5 per 1000. If tall women are more efficient than small women it must be because they are healthier and not simply because they are taller, since height alone should not confer any particular advantage. This implies that many women are small not because of heredity but because they are stunted and not fully grown — possibly as a result of faulty living conditions and deficient diet in the growing years. It seems a reasonable supposition that if stunting of the skeleton occurs, the body will generally be underdeveloped and will function at less than maximum efficiency and thus reproductive performance, along with other activities, will be adversely affected.

The effect of poor nurture in inhibiting the full expression of nature has received too little attention from geneticists and plant and animal breeders. The following two examples, one from the vegetable and the other from the animal kingdom, taken from an article by Leitch†, illustrate the effect of varying environment. If a dandelion is grown in a poor soil and in a cold climate it looks small and stunted, whereas in a fertile soil and at a higher temperature it grows tall and slender, with large green leaves. If the dandelion were an important food plant, the big succulent variety grown from the fertile soil would obviously be preferred, but since it is not, the question is possibly not of much account. Exactly the same happens if the edelweiss is transported to a low-lying fertile soil, but in so doing it loses the attractive gray coloring for which it is famous. It stretches out and becomes green and leafy; hence from the aesthetic point of view the fertile soil is a poor environment, no matter how good it may be from the point of view of growth.

The original wild pig at full growth is in shape more like the "improved" pig at birth than at maturity. That is to say, it has a relatively large head and a badly developed hind end. The characteristics that are valued by the farmer who sells the bacon are those that develop last, since the most prized parts are the loin and the hindquarters. From the commercial point of view, therefore, the rich diet and the protection from exposure, cold and damp afforded the domestic pig constitute a favorable environment. If a pig is underfed for the first half of its life and then given full rations it will put on weight, but the skeleton and muscles will not grow as they would have done if they had had the opportunity at the right time, and the extra food given will be laid down mainly as fat.

It appears, therefore, that growth potentials cannot be accelerated or slowed down at will. If we do not use these full potentials all the way along we will not obtain full development. The animal may attain the same ultimate weight, but the carcass will be different in shape and in composition. The well-grown pig will have the correct frame of bone and muscle to which the "finish" of fat can be added. Figure 4 shows the changes in shape that occur in man during growth. Essentially these are the same as in the pig, the hindquarters maturing last. If we retard the rate of growth sufficiently

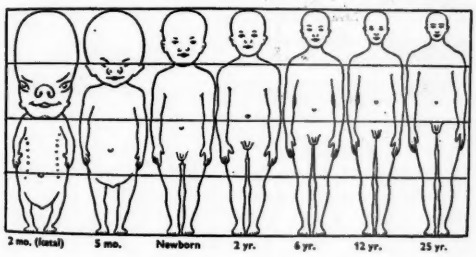

FIGURE 4. *Change in Proportions of Human Body During Development* (Stratz).

we obtain not only a small adult but an underdeveloped one, with normal or nearly normal-sized head, moderately retarded trunk and relatively short legs. In a dietary and clinical survey carried out in Aberdeen by the Carnegie United Kingdom Trust during the years 1937–1939, children were grouped according to the family expenditure on food per head. Height at the iliac crests was used as a means of measuring leg length, along with the height and weight, to find out which indicated most reliably the income group to which the child belonged. It was found that the cristal height was better than the total height for indicating the food-expenditure group; for children under twelve years of age, height was a better index than weight. Therefore, children coming from the higher income groups, in which the expenditure on food is greater, are characterized by their longer legs. The consciousness of this difference is universal and colors both literature and art. If the heroine is small it is expressly stated that she is "perfectly proportioned." Many modern works of art depict young women as having long, slender legs; in clothing advertisements in women's magazines the model is invariably tall and slender, with unbelievably long legs.

Since the legs suffer most in underdevelopment, their elongation and perfection of shape become the symbol of perfect growth, and since this is more likely to be achieved only in the best environment the length of leg comes to have some social signifi-

*"Fetal mortality," as used in this paper, is the stillbirth rate plus the death rate among babies prior to discharge from hospital.

†Leitch, I. Growth and health. *Brit. J. Nutrition* 5:142-151, 1951.

cance. That there is a close relation between height and social class can be seen by the following analysis (Fig. 5) of primigravidas in Aberdeen by height and social class of the patient's father. This has been used in preference to the social class of her husband, as it gives a better idea of the environment in which the patient has grown up. The

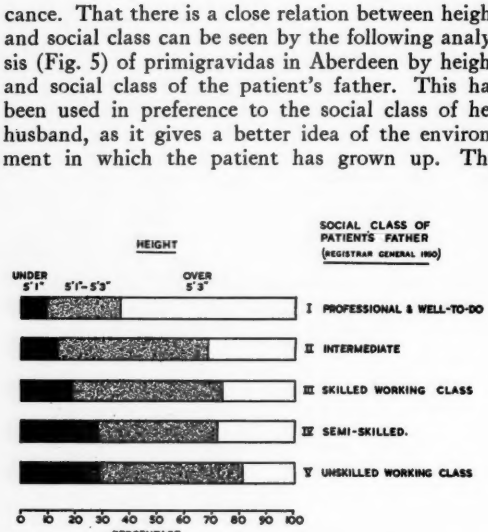

FIGURE 5. *Analysis of Primigravidas in Aberdeen by Height and Social Class of Father.*

figures show that as the environment deteriorates the percentage of small women increases. Figure 6 gives an analysis by height and occupation of the patient before marriage. It shows the same trend — namely, that as the social prestige of the job falls

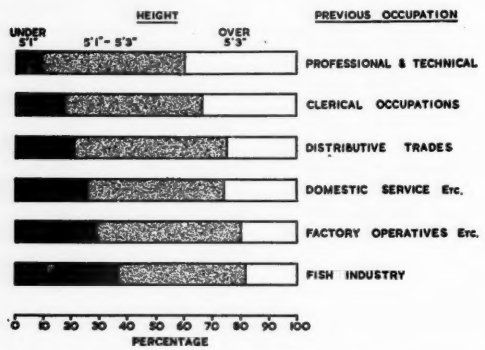

FIGURE 6. *Analysis of Height of Primigravidas by Occupation Prior to Marriage.*

so also does the height. Thirty-seven per cent of fish-workers are small (under 5 feet 1 inch). Fish work consists of standing in exposed sheds, cleaning and packing fish. It is hard and not very remunerative work, performed under rather disagreeable conditions, and it calls primarily for an ability to rough it. Figure 7 is an analysis of the height of primigravidas by age at the birth of the first child and by social class of the father. It shows that in women under twenty-five years of age the usual gradients of height can be seen, but in those over twenty-five years of age there are almost as many tall women in Social Classes IV and V as in I and II. The average size of the family of upbringing in Social Classes IV and V in this series was 2.5 children in those over twenty-five years of age, as compared with 5.5 in those under twenty-five years. From this it seems that parents in Social Classes IV and V who have small families can give their children a reasonably good education and good food, so that they grow tall and adopt the social habits of those in the upper social classes — one of which is to postpone the age of childbearing. In a group of 108 women medical students at the University of Aberdeen 58, or 53 per cent of the students, come

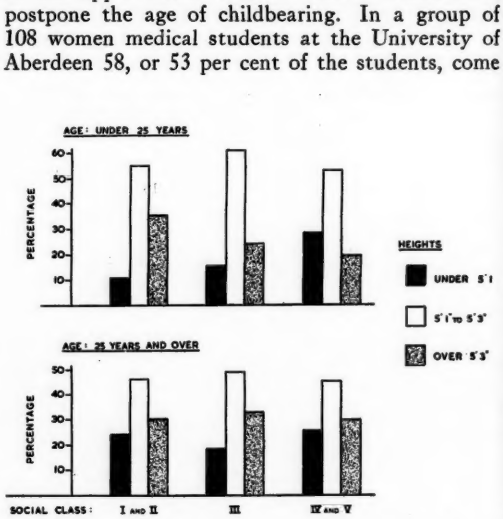

FIGURE 7. *Analysis of Height of Primigravidas by Age at Birth of First Child and Social Class of Father.*

from Social Classes I and II, and since in 1947 in Scotland only 12.6 per cent of the population belonged to these social classes, the students are obviously a privileged group. It is not surprising, therefore, that only 1 (1.7 per cent) was under 5 feet 1 inch. The environment in this group was probably optimal, since the parents would be of above average intelligence and have enough money to provide an abundance of food, good living conditions and good medical care.

Although there were more small women (6 per cent, or 3 out of 50) when the parents belonged to Social Classes III, IV or V, the relatively small percentage of short women suggests that lack of money does not of itself prevent good growth if the parents are ambitious enough to wish their children to go to a university. To do this, of course, they must limit the size of the family; this is confirmed by the fact that the average size of the family of upbringing was 2.4 children in this group.

To test more exactly our impression that tall women are on the whole much fitter and more co-

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operative and knowledgeable than small women, we have for some time been grading the hospital patients into one of 5 physical and functional classes, the assessment depending on the result of an examination carried out by the obstetrician at the time of the patient's first visit to the Antenatal Clinic. Generally speaking, the physical and the functional gradings were quite closely correlated, although in some very young patients the physical grading was higher than the functional — presumably because they still retained the "bloom" of youth. Table 3 shows that those in the lower physical grades have twice as high a fetal mortality as the others. In each height group, the poorer physical grades have a higher fetal mortality. Tall women and those of good physical grading have less than average prematurity. Table 4 shows that the prematurity rate is twice as high in those of poor physical grade as in the rest, and that the prematurity rate is higher in small than in tall women. The relation between physical grading and breast feeding was also studied; in primigravidas aged twenty to twenty-four, the incidence of bottle or partial bottle feeding rose steadily from 10 per cent in the highest physical grade to 26 per cent in the lowest. Follow-up one month later showed that the rate of failure at this stage was also greater in those in the low physical grades.

Despite the fact that health and physical fitness might be expected to deteriorate with increasing age, our finding is that the very young women (under twenty years) are on the whole poorer physical specimens than the older women. In the age group fifteen to nineteen, the incidence of small women under 5 feet 1 inch is higher than in any of the other age groups. Although most of the young women in the age group fifteen to nineteen are either eighteen or nineteen years of age when they become pregnant and have probably stopped growing, a few may not. That a few may not have stopped growing is not sufficient to account for the fact that there are more small women in the age group fifteen to nineteen. If women who had a first baby between the ages of fifteen and nineteen years are measured years later they are still found to be, on the average, smaller than those who had their first child at a later age. The fact is that women who have their first child before the age of twenty come, generally speaking, from the lowest economic groups and are therefore very stunted.

The fact that most of the small women are stunted received some confirmation from a study of the shape and size of the pelvis. Not unexpectedly, the size of the pelvis increases with the size of the patient. This is seen from Table 5, which shows the length of the anteroposterior diameter of the pelvic brim by height in a series of 100 tall and 100 small women who were examined by x-ray pelvimetry. The shape is also affected by height. Table 6 shows that the shape is affected by the size of the patient and by her physical grading. In each height group there is more flattening in those of poor physical grade. The assessment, although partly an estimate of the state of health at the time of pregnancy, also takes physical development into account, thus giving some indication of the childhood environ-

TABLE 3. *Obstetric Death Rates Per 1000 Births, by Maternal Height and Physical Grade, in 1792 Aberdeen Maternity Hospital Booked Primiparas (Excluding Twins).*

PHYSICAL GRADE	TALL (5 '4" AND OVER)	MEDIUM (5 '1"–5 '3")	SMALL (UNDER 5 '1")	ALL HEIGHTS
Very good (A)	17.1	29.4	64.5	28.2
Good (B)	41.4	41.7	34.5	40.1
Fair (C)	17.1	26.7	37.2	28.0
Poor, very poor (D and E)	50.0	80.6	92.3	81.6
All grades	28.1	34.6	50.9	36.8

TABLE 4. *Prematurity Rates (Per Cent), by Maternal Height and Physical Grade, in 1792 Aberdeen Maternity Hospital Booked Primiparas (Excluding Twins).*

PHYSICAL GRADE	TALL (5 '4" AND OVER)	MEDIUM (5 '1"–5 '3")	SMALL (UNDER 5 '1")	ALL HEIGHTS
Very good (A) ...	6.0	7.4	12.9	7.4
Good (B)	7.1	8.7	6.0	7.7
Fair (C)	8.5	5.0	12.2	7.8
Poor, very poor (D and E)	—	19.4	16.9	15.6
All grades	6.3	7.7	11.3	8.2

TABLE 5. *Influence of Height and Physical Grading on Conjugate Diameter of Pelvic Brim in 100 Tall and 100 Small Women (Bernard, 1952).*

HEIGHT	CONJUGATE DIAMETER OF PELVIC BRIM		ALL GRADES OF PHYSICAL HEALTH
	GRADE I PHYSICAL HEALTH	GRADE II PHYSICAL HEALTH	
	cm.	cm.	cm.
Tall (5 '5" and over).....	12.80	12.33	12.69
Small (under 5 '0") ...	11.01	10.71	10.77
All heights	11.90	11.50	

TABLE 6. *Percentage Distributions of Pelvic-Brim Shape (Nicholson's Classification) by Maternal Height and Physical Grading (Bernard, 1952).*

	ROUND OR LONG-OVAL BRIM SHAPE		FLAT OR TRIANGULAR BRIM SHAPE		ALL BRIM SHAPES
	%		%		%
Tall					
Grade I	94.8		5.2		100
Grade II		87.5		12.5	100
Small					
Grade I	73.6		26.4		100
Grade II		63.0		37.0	100

ment. In our experience cesarean section for disproportion is only occasionally necessary in women between 5 feet 1 inch and 5 feet 3 inches tall and almost never necessary in those of 5 feet 4 inches and over. It is clear, therefore, that from the point of view of fetal mortality, prematurity and lactation it is greatly to the advantage of the patient to be tall and to have high physical grading. These advantages are to some extent neutralized or obscured by the age factor when social groups are studied. The fetal mortality rises with age from twenty-five years, and the incidence of prolonged labor and instrumental delivery rises steadily from the age of twenty. It happens also that those in the worst physical condition and those brought up in the poorest homes marry and have children sooner than those who are healthy and tall and who as a rule come from good homes. This explains the small difference in fetal mortality in the two contrasting social groups that were mentioned earlier in this paper when primigravidas of all ages were compared. It also explains why a single age group must be studied before the superior performance of the upper economic groups can be demonstrated.

Age and Childbearing

So far we have been examining the effect of environment of fetal mortality, and it seems clear that a good environment, resulting in good health, means better reproductive performance. We have shown that the superiority is somewhat obscured by the fact that women from a good environment are usually older at the time of the first birth than those brought up in a poor environment. We shall now

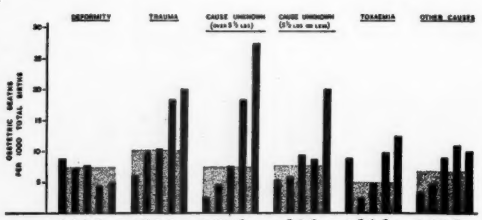

FIGURE 8. *Effect of Age on the Various Causes of Fetal Mortality.*

discuss the influence of age on childbearing in more detail. Figure 8 shows the effect of age on the various causes of fetal mortality in a group of 9790 booked primiparas, and Figure 9 shows the relative importance of some of these causes of fetal death in each age group. In the age group fifteen to nineteen the most important causes of fetal death are toxemia, fetal deformity and prematurity. In the age group thirty to thirty-four, — a group to which many in Social Classes I and II belong, — these causes are relatively unimportant when compared with birth trauma and unexplained intrauterine death at or about full time — causes that in the

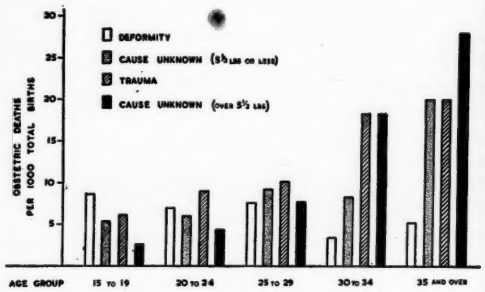

FIGURE 9. *Relative Importance of Some Causes of Fetal Death, by Age Group.*

younger age group are relatively unimportant. Figure 10 shows that youth is an important factor in labor. A spontaneous delivery by the vertex in less than twenty-four hours seems to be a reasonable definition of normal labor. The incidence of

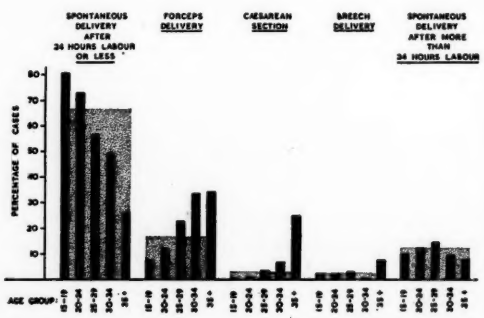

FIGURE 10. *Type of Labor in "Booked" Primiparas, by Age.*

such deliveries among primigravidas in the present study fell from 80.7 per cent in the age group fifteen to nineteen to 26.6 per cent in those of thirty-five years or more. Conversely, the percentage of labors lasting forty-eight hours or more rose from 2 per cent in the youngest to 8.6 per cent in the oldest age group. The incidence of forceps delivery and cesarean section rose steeply with age, demonstrating very strikingly the great advantage of youth in ensuring an easy and short labor. In the management of a labor likely to end spontaneously, an episiotomy is preferred only if it seems probable that the perineum is about to tear. The incidence

of intact perineums in those primiparas who had a spontaneous delivery fell from 55 in the fifteen-to-nineteen age group to 36 per cent in those between twenty and twenty-four. The young women seem able, therefore, to stretch the perineum without tearing and without the necessity for an episiotomy much better than those who are only a few years older. The only serious difficulties encountered in labor in the fifteen-to-nineteen age group result from a contracted pelvis. If the pelvis is grossly contracted an obstructed labor will occur even in the presence of the most efficient uterine contractions and bearing-down efforts. In the older age groups, difficult and prolonged labor frequently occurs, in the absence of contracted pelvis or occipitoposterior positions, as a result of disordered uterine action and inability to bear down effectively in the second stage. Not only do the older women have a more difficult labor, but the effect on the patient is much more pronounced and lasting. In a series of 1178 primiparas having a difficult first labor between the years 1938 and 1947, the percentages of those who had no more children when followed up in the years 1950–1951 were 7.4, 20.6, 26, 46.9 and 73.2 in each five-year age group respectively. The average was 29.4. Table 7 shows that those who are over twenty-five years of age at the time of the birth of the first child are twice as likely to have no more children than those under twenty-five. A glance at the reasons for this shows, as one would expect, that involuntary sterility is higher in the older women and that some thought they were too old to have any more. Many more deliberately refrained from having another child. In some the reason for this was not clear, but fear of labor and general over-anxiety were much more common in the older age groups. Some talked about the terrible ordeal they had endured, when in fact the labor was more or less normal. The following letter is an example:

> I have had no other child since 14.9.46 and have no intention of having another one if I can help it (touch wood). I am certainly taking all precautions and my husband agrees with me in this matter.
>
> First of all, after my child's birth I was extremely weak and never recovered my full strength until three years after. No one likes to be a semi-invalid, and that was what I was, in fact it was ages before I could push my baby's pram any distance, and it was an effort to stand up straight. Before my baby was born I was very healthy and seldom had anything wrong with me, apart from a cold, and I could count the days I have been in bed on one hand since I left school. Health is very precious and worth more than anything else.
>
> I do think that if I had a little more assistance when I was in labour I wouldn't have been so weak after it.
>
> You call it a spontaneous birth. I do not know what that means, but I felt at the time I didn't have enough strength to go on so long. Pain is nothing. One can put up with that. There is a lot to be said for the old-fashioned doctors. I am sure they would have been a lot more helpful.
>
> So for the sake of all the mothers-to-be, about 35 years old to 40 years, be a little more considerate of them. Our bones are set, I think, especially if we lead a strenuous life — dancing, cycling, and hiking, etc. and you will have a lot more babies.
>
> I intended to have more, but not now.
>
> Excuse criticism, but I feel very strongly about it.

In this case, the labor was classified as difficult only because it lasted thirty hours. During the first twenty-four hours the pains were very slight, and when pains were properly established the progress was rapid and delivery spontaneous.

Housing and financial worries were also more frequently given as a reason by the older women despite the fact that, on the whole, their social circumstances are much superior to those of the younger women. They are also much more concerned about maintaining standards and giving their one child "every advantage."

TABLE 7. *Follow-Up in 1950-1951 of Cases of Difficult First Labors (1938-1947).*

	AGE UNDER 25 (574 CASES) %	AGE 25 AND OVER (604 CASES) %
No further pregnancy	20.4	39.9
Reasons for no further pregnancy		
Widowed or divorced	2.1	3.1
Ill health	1.2	2.3
Fear of labor, neurosis	2.6	6.3
"Too old"	—	2.7
Financial reasons	1.6	3.6
Social reasons (mainly housing)	5.6	7.1
Voluntary, ? cause	5.2	8.3
Involuntary	1.9	4.5
Miscellaneous other reasons	0.2	2.0

CONCLUSIONS

The evidence of this research shows that much inefficiency in reproduction is the result of impaired growth and health and of deterioration associated with aging. Since the well-to-do tend to be healthy and well grown but to reproduce late and the poorer classes to be less healthy but to reproduce early, the social differentials are not clear-cut unless the age factor is taken into account. It is clear that good physique, health and education and early marriage are ideal for efficient reproduction. The two main problems in preventing reproductive inefficiency are the improvement of social conditions, so that stunting of growth and malnutrition decrease, and the removal of barriers to early marriage among those who already live in a good environment. Great progress toward solving the first of these problems has been made in Britain since 1938 — a progress that is the more remarkable because it took place during World War II and its aftermath.

Social improvement must be guided by continued research. It is of great importance to discover how far the rise in fetal mortality and the incidence of disordered uterine action that are associated with age are inevitable and how far the process of aging can be retarded by the provision of a suitable environment.

In this connection, it is also necessary to consider how far an environment that is suitable for full physical and intellectual development is compatible with race survival. This problem become more important as the standard of living rises and the family is more and more planned. The present trend among educated persons is to reduce the number of children in the interests of a still higher standard of living for these children, until this group of society fails to reproduce itself. Since professional women tend to marry professional men, they are likely to have children with intelligence above the average, but in the present state of society many of them postpone starting a family and then restrict the total number of children to an extent that ensures a decline in this valuable population. From the strictly obstetrical point of view, difficult labor is a significant contributory factor in the decision to limit the family, though not the most important one. Research should therefore be directed toward determining the cause of prolonged labor due to disordered uterine action.

I trust that I have succeeded in demonstrating the importance of a preventive outlook in obstetrics. The relatively high fetal mortality and prematurity rates associated with poor health and the high incidence of difficult labor found in elderly primiparas can be mitigated but cannot be satisfactorily dealt with, even by the highest standard of obstetric art and skill.

I wish to acknowledge help received by the director and staff of the Social Medicine Research Unit, Medical Research Council (Great Britain), in some of the researches dealt with in this paper.

CORTISONE AND ACTH AS AN ADJUNCT TO THE SURGERY OF CRANIOPHARYNGIOMAS*

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THE surgical management of craniopharyngiomas, whether radical or conservative, has always been hazardous. Gordy, Peet and Kahn[1] reported a series of 51 cases in which the operative mortality was 41 per cent, due principally to severe hypothalamic reactions incident to the surgical manipulation. Grant,[2] in summarizing the results of 40 operations on 30 patients, found a case mortality of 35 per cent and an operative mortality of 25 per cent. He noted generalized endocrine glandular atrophy in many of the fatal cases and stated that "the problem in surgical treatment of craniopharyngioma is threefold: to escape hyperthermia from damage to the hypothalamus, to prevent complete glandular collapse after operation, and to avoid damage to the carotid artery." Love[3] reported a 40 per cent operative mortality in a series of 96 cases, but no details of the immediate cause of death or the time relative to operation were given. Ingraham and Scott[4] reported only 1 operative fatality in 16 initial craniotomies for craniopharyngiomas in children. In none of these patients was complete extirpation attempted. It should be noted also that this relatively low mortality may coincide with the rarity of gross endocrine disorders in this age group. In all these series the tests today available for evaluating preoperatively the functional capacity of the pituitary adrenal system were, of course, not employed.

It is apparent that most of the operative complications in the treatment of craniopharyngioma result from the proximity of the lesion to the pituitary gland and the hypothalamus. Manipulation in this region is perilous at all times, but the danger is accentuated in the majority of these cases because of the added depression of the normal potential pituitary-adrenocortical response to stress. The physiology involved is complex and in detail is not within the scope of this paper. The major complications of surgical importance include disturbances of vasomotor control, temperature regulation, salt and water metabolism and carbohydrate metabolism. The first two of these have in the past constituted the principal complications encountered during or immediately after operation. The latter two assume major importance in the late postoperative recovery.

The availability of adrenal substitution therapy in the form of cortisone and ACTH has offered a means of preventing and controlling most of the complications, especially in patients with impairment of the normal pituitary-adrenal response. It was first employed in this department as an adjunct to the surgery of a pituitary adenoma.[5] It now seems worth while to record experiences with 4 children undergoing operation for craniopharyngioma in whom these drugs were used. One of them received ACTH and 3 were given cortisone. Obviously, many patients with craniopharyngiomas have tolerated partial and, perhaps rarely, complete

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extirpation of these lesions without important postoperative hypothalamic or endocrine crises. These 4 cases cannot, therefore, be considered statistically significant. However, in comparison with previous experiences, the stable course of each of these 4 successive patients appears to confirm the theoretical value of these drugs in the surgical management of suprasellar tumors.

Case Reports

Case 1. O. T., an 11-year-old girl, was first admitted to the Children's Medical Center in May, 1950, because of retarded physical growth, easy fatigability, poor appetite and a history of 2 episodes of coma associated with high fever and vomiting. Examination revealed a girl of small stature with pallor of the left optic disk and constriction of the left visual field. X-ray examination showed suprasellar calcification and an enlarged sella turcica.

After subcutaneous injection of 0.15 cc. of 1:1000 epinephrine hydrochloride, the circulating eosinophils changed from an initial level of 99 to 132 cu. mm. in four hours. This negative response suggested marked anterior-pituitary deficiency.* She was started on ACTH, 10 mg. intramuscularly, every six hours. Two days later no circulating eosinophils were observed. Because the basal metabolic rate was −28 per cent, thyroid extract, 30 mg. per day, was begun. Thyroid extract and ACTH were continued for 1 week. On the evening before operation 5 mg. of desoxycorticosterone was given intramuscularly in an attempt to stabilize the blood pressure, which was 90/60.

At operation the left optic nerve was found to be flattened and displaced upward by a large cystic mass presenting both medially and laterally to the nerve. Fifteen cc. of chocolate-colored fluid containing cholesterin crystals was aspirated from the cyst; a large portion of the capsule, together with solid tumor within the capsule, was removed.

The blood pressure during the first part of the procedure was low, the systolic pressure varying from 60 to 70 mm. of mercury. During the latter half of the operation, which lasted 3 hours, the blood pressure rose to 88/60 and remained there. The pulse rate was 150 at the beginning but soon stabilized at 120.

The postoperative course was smooth, with no elevation of temperature above 101°F. and with normal blood pressure and pulse throughout. The patient was continued on ACTH postoperatively according to the following regimen: 10 mg. every 4 hours for 6 days; 10 mg. every 6 hours for 2 days; 10 mg. every 8 hours for 3 days; and 10 mg. twice daily for 1 day. Thyroid extract was continued for 1 week and then stopped. Transient diabetes insipidus appearing on the fourth day was easily controlled by several injections of pitressin. The wound healed well, and the patient was discharged on 3.0 gm. of sodium chloride in addition to her normal salt intake. During her 12 days' postoperative hospitalization she gained 8 pounds.

After discharge recurrent bouts of vomiting and weakness occurred, believed to be caused by adrenal insufficiency. Each episode was controlled by a course of intramuscularly given cortisone. Therefore cortisone pellets were implanted subcutaneously; after this procedure she gained weight (20 pounds) and showed considerably more vigor than previously. After dissolution of the pellets (in about 4 months) she was placed on cortisone acetate, 12.5 mg. daily, and has continued to do well, with only slight skeletal growth.

Comment. There is no doubt of the hypopituitarism that existed preoperatively. It is believed, therefore, that without artificial stimulation of her adrenocortical secretion her physiologic state would have been much more precarious. The disappearance of circulating eosinophils after ACTH administration for 2 days indicates that the adrenal cortex was still capable of responding and had therefore not undergone any marked involution. The postoperative episodes of nausea and vomiting with weakness and listlessness, relieved by additional salt intake and a small amount of cortisone daily, make it clear that this patient was suffering from adrenal insufficiency. It should be emphasized that once long-term substitution therapy with cortisone is begun it must be continued indefinitely, since it favors further pituitary involution. Impairment of growth-hormone production by the anterior pituitary lobe is obviously present in this patient, but at present no substitution therapy is available to combat this deficiency. Since her thyroid function appears adequate, thyroid medication is not only unnecessary but an unwarranted risk in the presence of adrenal insufficiency.

*The dose employed was less than the 0.3 cc. recommended in the original epinephrine test.

Case 2. O. M., a 10-year-old girl, was first admitted in October, 1947, because of visual failure during the previous 2 years and 2 weeks of headache, nausea and vomiting. Examination showed optic atrophy, absent pupillary reflex, blindness on the right and papilledema on the left. X-ray films revealed suprasellar calcification. On the day following admission she suddenly went into an episode of peripheral vascular collapse and apnea, which was relieved by a ventricular tap. Her serum chloride was reported as 72 milliequiv. per liter on this day and over the next week rose to 100 milliequiv. through the addition of salt to the daily intake.

On the 9th hospital day, with support of adrenocortical extract and desoxycorticosterone, ventriculogram and craniotomy were performed. Exploration of the optic chiasm revealed no tumor in this region. A needle was introduced through the right lateral ventricle and a craniopharyngioma cyst was encountered and emptied. No further exploration was deemed advisable, although her condition had remained quite stable.

The patient was readmitted 4 times during the next 4 months, each time because of nausea, listlessness and malaise; each time her symptoms were relieved by aspiration of the cyst. In April, 1948, a bilateral Torkildsen procedure (ventriculocisternal shunt to bypass the ventricular obstruction) was performed.

She returned to the hospital in June, 1951, because of recurrence of headache and increasing fatigability. Examination revealed blindness on the right and 20/30 vision on the left. Her body weight was 55 pounds.

Laboratory findings, including serum electrolytes, were normal. The circulating eosinophils dropped from 82.5 to 44.0 per cu. mm. in response to 0.02 cc. of 1:1000 epinephrine hydrochloride. This 46 per cent fall approaches the normal range (50–85 per cent).

She was started on cortisone on the 5th hospital day; ventriculography and aspiration of the cyst were performed on the following day without event. It was then decided that exploration of the tumor should again be attempted. This operation was supported by the following regimen: cortisone, 100 mg. intramuscularly, on the night before operation; cortisone, 100 mg., on the morning of operation; during operation 5 per cent D/W and whole blood by constant infusion with neosynephrine as needed for hypotension. The postoperative regimen was; cortisone, 20 mg., every 6 hours for 2 days; cortisone, 10 mg., every 6 hours for 2 days; and cortisone, 5 mg., every 6 hours for 2 days. At operation, which lasted 3½ hours, the cyst was widely opened through a transventricular approach and a portion of the wall removed. The solid part of the tumor was posterior and inferior, and although it could not be removed completely an estimated 1/3 was excised, with considerable manipulation in the region of the third ventricle and hypothalamus. The patient's chart during operation remained fairly stable. There was a mild transient drop of blood pressure from 90/50 to 80/30 for about 30 minutes. The pulse and respirations were constant. At the end of the operation the rectal temperature was 92.8°F., but during the first 5 hours postoperatively it rose to normal limits, where it remained thereafter. During the same period there was a temporary elevation of blood pressure to 124/76, but this quickly returned to preoperative levels.

The patient gradually recovered from the operation; except for some mental confusion and lethargy, which subsided over the next two weeks, her course was uncomplicated.

Comment. The preoperative epinephrine test, though somewhat below the normal range, did not reveal a clear-cut ACTH deficiency, but in view of her general debility substitution therapy was undertaken to combat the impending operative stress. That some degree of physiologic imbalance was precipitated is indicated by the striking drop in body tempera-

ture during operation, but this was of short duration, and the rapid fluctuations between hypothermia and hyperthermia, so commonly seen after third-ventricle surgery, did not occur. Since discharge the patient has not required substitution therapy.

CASE 3. D. Q., a 5-year-old girl, was admitted in January, 1951, because of progressive blindness associated with suprasellar calcification. Two years previously she had exhibited increased intracranial pressure and ataxia; posterior-fossa exploration was undertaken. A small mass in the fourth ventricle was excised and a Torkildsen procedure carried out. Because the possibility of a pathological diagnosis of medulloblastoma was entertained the operation was followed by x-ray therapy consisting of 3000 r to the posterior fossa and 1000 r to each side of the head. Eight months later, with return of symptoms, another course, consisting of 1000 r to the posterior fossa and to each side of the head, was given. On subsequent review of the histologic sections, however, the diagnosis was changed to congenital hamartoma.

Examination on the present admission showed almost total loss of vision in the right eye and a temporal hemianopsia on the left. Ventriculography confirmed the presence of a large suprasellar mass bulging into the enlarged right lateral ventricle. Tapping of this cystic mass released 150 cc. of typical oily fluid containing cholesterin crystals. She was discharged in good condition and was followed closely.

Three months later her appetite became poor, she became listless and there was again evidence of increased intracranial pressure. The epinephrine test showed no fall in circulating eosinophils on one occasion and on another showed a drop of only 30 per cent, suggesting anterior-pituitary ACTH insufficiency. In contrast, an injection of 25 mg. of ACTH (ACTH test) was followed by a 65 per cent fall in circulating eosinophils.[7] This essentially normal adrenal response indicated the presence of normal adrenal cortex with inadequate ACTH reserves.

It was thought that the patient had sufficient adrenal function for ordinary maintenance but secretion would be inadequate under stress. Therefore, supportive hormonal therapy was given for surgical exploration according to the following plan: cortisone 20 mg. every 6 hours for 2 days preoperatively and adrenal cortical extract, 35 cc., in constant infusion during surgery. The postoperative regimen was: cortisone, 25 mg., every 6 hours for 2 days; cortisone, 15 mg., every 6 hours for 2 days; and cortisone, 5 mg., every 6 hours for 2 days.

At operation the right optic nerve was found to be compressed by a cystic structure medial to it. When this cyst was entered it was seen to contain golden-yellow fluid with flecks of calcium. A portion of the wall about 2 cm. in diameter was removed. A thin layer of adherent solid tumor extended over the chiasm and posteriorly in the hypothalamic region. No attempt was made to remove this. The operation lasted 4 hours.

The patient's course during and immediately after surgery was extremely smooth, without unusual fluctuation of vital signs. The systolic blood pressure varied from 90 to 100 mm. of mercury; the diastolic pressure ranged from 60 to 70. The pulse was about 130 during the first part of the operation and 115 during the latter part. Respirations were stable. The body temperature did not exceed 101.6°F. postoperatively and was not subnormal. She recovered rapidly and was discharged home after 2 weeks.

Comment. Considerable local manipulation in this patient was not accompanied by any untoward reactions during or after the surgical procedure. The adrenal cortical extract used during surgery was not really indicated; this should be reserved for patients in moderate shock as a means of rapid administration of cortical hormone. This patient has not required any postoperative substitution therapy.

CASE 4. K. M., a 3 9/12-year-old girl, was first admitted in October, 1950, because of fever, extreme drowsiness and generalized muscle tremor associated with an acute pharyngitis. Neurologic examination was entirely negative except for marked somnolence. X-rays showed suprasellar calcification consistent with craniopharyngioma. The visual fields were normal. An epinephrine test showed no lowering of the circulating eosinophils, which remained at 66 per cu. mm. The fever and pharyngitis cleared on antibiotic treatment, and she was discharged.

She was followed closely and remained asymptomatic until 9 months later, at which time she returned with bitemporal hemianopsia. Exploration of the suprasellar tumor was undertaken with preoperative and postoperative administration of cortisone on the following regimen: cortisone, 100 mg. intramuscularly, on the night before operation and cortisone, 100 mg, on the morning of operation. The postoperative regimen was: cortisone, 25 mg. every 6 hours for 2 days; cortisone 15 mg. every 6 hours for 2 days; and cortisone 5 mg. every 6 hours for 2 days.

At operation, which lasted 3½ hours, a cyst anterior to the chiasm was aspirated. At this point the blood pressure, which had risen from its original level of 100/80, reached a peak of 168/90. Thereafter, during the remainder of the operation it remained steady at 150/100. At the end of the procedure it suddenly dropped to 100/80 and remained steady after that time. The respirations ceased for a few seconds at the time of the cyst aspiration but then returned and were stable. The pulse rate fluctuated between 100 and 150 during the operation but immediately afterwards remained between 100 and 120. The highest recorded temperature was 101.8°F. postoperatively, and there were no sudden fluctuations.

Postoperatively she recovered rapidly and was discharged on the 7th postoperative day.

Comment. Aside from the epinephrine test 9 months prior to operation there was no evidence of any hormonal imbalance or deficiency in this patient. It is impossible, therefore, to evaluate her smooth postoperative course in relation to the use of cortisone.

DISCUSSION

Some degree of endocrine dysfunction is probably present in nearly all patients with craniopharyngioma, although in children it is less likely to be grossly apparent than in adults. Each of the cases presented exhibited some degree of endocrine deficiency; this varied from the immediately apparent Lorain type of growth arrest in Case 1 to the subtle changes detected only on laboratory testing in Case 4.

The uncomplicated postoperative recovery of each of these 4 patients suggests that adrenal substitution therapy is a useful adjunct in the surgical management of craniopharyngiomas in children. The importance of replacement therapy may be even greater from adolescence to middle age, because endocrine deficiency is usually more pronounced in these patients. This is apparently a reflection of chronic pressure on the diencephalopituitary axis. Hormonal support might well be extended to any surgery in the parasellar region, especially if a mass lesion is present that may have compromised the function of this area by pressure or vascular impairment. Such therapy is prophylaxis against the complications of operative trauma to the hypothalamus and pituitary gland. A particularly desirable effect of cortisone and ACTH is the beneficial action on development of cerebral edema. The action of these drugs, — especially cortisone, — contrasts with that of desoxycorticosterone.[8] It is believed, however, that adrenal substitution therapy should not be limited to cases of frank pituitary insufficiency as demonstrated by a negative epinephrine test but should be given to all patients with craniopharyngioma undergoing exploration unless specific contraindication exists.[9]

In the choice of therapeutic agent, cortisone has the advantage of effectiveness irrespective of the state of the pituitary-adrenal system. ACTH, on the other hand, requires a responsive adrenal cortex. This drug has the advantage of stimulating the normal production of adrenal steroids; thus sudden withdrawal does not lead to adrenal insufficiency of the extent seen after sudden cortisone withdrawal. The dosage of both drugs, however, should always be decreased gradually to avoid an adrenal crisis due to abrupt discontinuation of hormone therapy — a suppressed adrenal cortex in the case of cortisone and a rapidly involuting one in the case of ACTH.

Sodium intake need not be restricted during therapy, since one is usually dealing with hypotensive persons. With cortisone there is less salt retention than with ACTH.

The relatively short period during which large doses of hormone (200 mg. of cortisone or 100 mg. of ACTH per day) are administered to these patients precludes the occurrence of most of the complications that may follow long-term therapy with these agents.[10] In the reported cases no untoward effects of the hormonal therapy were noted.

Cortisone

Cortisone has the advantage of quick action. It should be started no more than twenty-four hours before surgery and discontinued within a week in order to minimize interference with wound healing. This complication is usually seen only with larger dosages than were used in these patients; we have noted no such effect. In patients requiring continued substitution therapy the dose should be reduced to 25 mg. per day as soon as possible. A tentative schedule for the administration of cortisone acetate is suggested as follows: 100 mg. on the night before operation; 100 mg. on the morning of operation; 25 mg. every six hours for one day; 25 mg. every eight hours for two days; 25 mg. every twelve hours for two days; and 25 mg. per day for two days.

The intramuscular route should be used because of the more prolonged effect as compared with that of oral administration.

ACTH

If ACTH is employed, more prolonged administration is required. It should be started at least five days before surgery to obtain adequate activation of the partially involuted adrenal cortex and ensure sufficient circulating adrenal hormone at the time of maximal stress. Here, too, dosage should be reduced as soon as possible after surgery. The following schedule is suggested for administration of this drug: 20 mg. every six hours for at least five days preoperatively; 20 mg. every six hours for two days postoperatively; 20 mg. every 8 hours for two days; 20 mg. every 12 hours for two days; and 20 mg. every day for one day.

Summary

The use of cortisone and ACTH in the surgical management of craniopharyngioma in 4 children has been described. The stable course during and after surgery of each of these patients has been emphasized, and the physiologic basis for the use of the agents has been outlined. Suggested therapeutic schedules are presented.

Since the preparation of this paper 2 other patients with craniopharyngiomas have been treated with cortisone according to the proposed regimen. A single operation was performed on one of these patients, whereas the other underwent a three-stage removal of his tumor. The postoperative course in each instance was as satisfactory as those described in the paper.

The authors are indebted to Dr. Peter H. Forsham, associate in medicine, Peter Bent Brigham Hospital, for his assistance in directing the endocrine therapy of the patients described.

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CLINICAL NOTE

MILIARY TUBERCULOSIS DEVELOPING DURING PREGNANCY*

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MILIARY tuberculosis is uncommon in adults. Its occurrence complicating pregnancy is an especially rare finding. The case to be presented is of unusual interest because only one other case of miliary tuberculosis developing during pregnancy has been reported[1] and because the infant survived and at twelve months of age is known to be in excellent health. The mother died on her twelfth post-partum day.

Miliary tuberculosis is frequently observed below the age of two years. Despite antibiotics, the mortality has continued high. Miliary tuberculosis complicated by meningitis has shown an even higher mortality rate.

In 1938 a review of the European literature by Falkenflet[2] disclosed 44 cases of miliary tuberculosis complicating pregnancy. In these cases the disease was a complication of the puerperium. Most of the reports are from Scandinavian authors, and one concludes that in all instances the disease was fatal to the mother and also to the infant, although some infants survived for periods ranging from a few weeks to several months. The American authors Spencer, Spino and Silverman[3] recently reported a case of miliary tuberculosis in pregnancy. They state that they have been unable to find any previously reported cases in the recent literature. In their case the mother aborted spontaneously at five and one-half months, the baby dying thirty minutes after delivery. The mother recovered from her miliary tuberculosis, only to die of tuberculous meningitis and pyelonephritis nine months later. Jameson,[4] however, reports a patient of Fraser who miscarried a five-month stillborn fetus and died one and one-half hours after delivery.

"Necropsy showed tuberculous laryngitis, bilateral, tubercular bronchopneumonia with cavitation in the right apex, intestinal tuberculosis, and miliary tuberculosis of the spleen and diaphragm. The uterus revealed miliary tubercles in the placental site."[5]

In the following case report the miliary tuberculosis improved by x-ray, the mother gave birth to a child who has shown no signs of tuberculosis and the mother died from meningitis during the puerperium.

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CASE REPORT

E. M., a 25-year-old gravida II, para I, had her last menstrual period on January 7, 1950. Fetal activity was noted in mid-May. The expected date of confinement was October 14, 1950. The patient was first seen on April 27, 1950. Her past history was entirely negative. She had had 1 previous pregnancy, with a short normal labor and delivery of a 7½-pound infant in July, 1947. She breast fed the baby for 6 months. She had had no miscarriages. Her menstrual periods began at the age of 14 and were regular every 30 days with a 4-day flow, with slight cramps at the onset. She had had fairly severe nausea during the first trimester but only occasional vomiting. The nausea had subsided when she was first seen. General physical examination and laboratory findings were normal. Her pregnancy was uneventful until July 17, 1950, when she developed chills, fever, burning urination and bilateral costovertebral tenderness. The urine was loaded with white blood cells. A diagnosis of pyelitis was made, and she was treated with penicillin and sulfadiazine. Her temperature was 103°F. and her pulse 108. After 3 days' treatment at home without improvement she was transferred to the hospital. She was obviously seriously ill. At this time she showed herpetic lesions of the upper lip. There was slight abdominal distention and left costovertebral tenderness. A pregnant uterus extended halfway from the umbilicus to the xiphoid. A fetal heartbeat at a rate of 150 per minute was heard in the left lower quadrant.

During her stay in the hospital she ran a spiking temperature up to 104°F. in the afternoon. She insisted that she had no cough and no expectoration. X-ray examination of the chest showed unmistakable miliary lesions crowding both lung fields. The red-cell count was 2,980,000, the white-cell count 5400; the differential showed 72 per cent segmented polyps, 3 per cent band forms, 24 per cent lymphocytes and 1 per cent large mononuclear leukocytes. On July 28, 1950, she was given a blood transfusion; the red-cell count was noted to be 3,310,000 and the white-cell count 11,800. On August 1, 1950, after a second transfusion, the red-cell count was 3,430,000 and the white-cell count 7000. She was somewhat improved after the transfusions. Blood cultures were negative for pyogenic organisms. Widal tests were negative. Tuberculin skin tests (Mantoux) in three dilutions were negative. The first chest x-ray film was not satisfactory, but the second plate was typical of miliary pulmonary tuberculosis. She was therefore given streptomycin, 0.5 gm. twice daily, and transferred to Sassaquin Sanatorium.

During her stay at the tuberculosis sanatorium she improved only slightly, was nauseated much of the time and required intravenous feedings on many occasions. Two weeks after admission to the sanatorium chest x-rays revealed definite regression of the miliary lesions, particularly in the upper ⅔ of the lung. A repeat plate on August 30, 1950, showed even further regression. During this time her temperature peak dropped to 102.3°F. She had now developed sputum, which was invariably negative for tubercle bacillus. A urine concentrate inoculated into a guinea pig proved positive for tubercle bacilli. Her vomiting spells continued to increase. Shortly after admission she began to complain of persistent frontal headaches. On August 11 she was seen by a neurologic consultant, who performed a lumbar puncture. The findings were consistent with tuberculous meningitis. She also developed some difficulty in swallowing, complaining of a lump in her throat. A laryngoscopic examination revealed disease of the epiglottis. A biopsy of the epiglottis, taken on August 29, was reported positive for tubercle bacilli. On September 18 she was transferred from Sassaquin Sanatorium to St. Luke's Hospital, in impending labor. On September 19, after an easy normal labor, she had a multiparous normal delivery with a median episiotomy under light nitrous-oxide oxygen anesthesia of a 5-pound 3-ounce living female infant, who breathed and cried promptly. The placenta appeared grossly normal but was sent to the Pathology Laboratory. Gross and microscopical examination revealed tuberculosis of the placenta. A guinea-pig inoculation of amniotic fluid was reported as negative.

After delivery the patient continued weak, with nausea, lack of appetite and rising temperature and pulse. Her frontal headaches were severe. Within the week she developed twitching, episodes of coma and delirium. Lumbar-puncture findings were consistent with tuberculous meningitis. Streptomycin therapy was continued. She received daily intravenous injections of glucose and amino acids. On September 30 she had a slight convulsion. On October 1 she developed a convulsion, characterized by twitching of all extremities and face, that lasted for about 3 hours. She lapsed into deep coma and died.

Permission for a limited autopsy was obtained. The most interesting observation at the autopsy was that the miliary seedings throughout the lung fields were not nearly as numerous as those seen in the original chest x-ray films. Small tubercles were found in almost all organs of the body.

The infant was placed on small amounts of streptomycin as a prophylactic measure (50 mg. 3 times daily) for 3 months. Twelve months later she is well and has a negative tuberculin skin test.

The patient, an intelligent woman, had vehemently denied a family history of tuberculosis or any contact with tuberculosis throughout her life. Investigation some months afterwards in another part of the country revealed that the patient's father had suffered from chronic pulmonary tuberculosis and had died in a tuberculosis sanatorium. The patient had been very fond of her father, and had been with him during much of his illness. The patient's husband was completely unaware of the family history of tuberculosis.

Comment

The feature of this case is its rarity. Miliary tuberculosis and tuberculous meningitis are seldom observed as complications of pregnancy; a normal infant, who was born twelve months later, is entirely well, with no signs of tuberculous infection. It may well be that this is the first case in which streptomycin was given to an infant as a prophylactic measure.

Summary

A case is presented of miliary tuberculosis and tuberculous meningitis developing during pregnancy. Streptomycin caused some regression of the miliary tuberculosis but had no effect on the tuberculous meningitis; a living female infant was born, treated prophylactically with streptomycin and shows no signs of tuberculous infection at the age of twelve months. The mother died from tuberculous meningitis twelve days post partum.

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MEDICAL PROGRESS

SOME PRACTICAL ASPECTS OF CANCER PREVENTION (Concluded)*

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NEW YORK CITY

Carcinoma of the Skin

Incidence

The difference between morbidity and mortality data in cancer of the skin reflects the curability of this form of malignant disease. In 1940 in the United States the incidence of skin-cancer cases per 100,000 among white males and females was 38 and 28 respectively, whereas the mortality per 100,000 white population was 2.6 and 1.7 respectively.[209] In 1948, 2111 males and 1451 females died of cancer of the skin in the United States, whereas 522 males and 46 females died from cancer of the lip and 35 died from cancer of the scrotum in the United States.[21] Among 4839 cases of cancer of the lip collected from the world literature, 94.2 per cent involved the lower lip.[210]

The incidence of skin cancer is higher in rural than in urban areas. At the Ellis Fischel Hospital in Missouri, which serves largely a farm population, 40 per cent of cancer admissions had cancer of the skin.[211] Comparative incidence rates per 100,000 showed 116 for the south, 49 for the west, and 23 for the north among males; the respective data for females showed 70, 34 and 18.[209] Skin cancers occur more commonly among the whites. The incidence rate for skin cancer in whites is about 7 times as great as that for Negroes.[212]

Suspected Etiologic Factors

As early as 1894, Unna, in describing the "Seemannshaut," suspected that sunlight was of etiologic significance in the production of skin cancer.[213] This concept was also emphasized by Hyde in 1906[214] and has been upheld by most workers. Blum[215] has done much to clarify the effect of ultraviolet light on the production of skin cancer. Atkin and his associates, in a study of death records of skin-cancer patients in England and Wales, reviewed 5915 cases of cancer of the skin and lip covering the period 1911 to 1944,[216] comparing agricultural workers, miners and professional workers. They found the highest incidence in agricultural workers, with a percentage ratio of 142.4 as compared to 94.4 for miners and 47.5 for professional men. Among the agricultural workers,

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gardeners and garden laborers were highest, with a ratio of 198. Civil engineers and surveyors were highest among the professional men (121.3); among the miners, the metal miners were the highest (118.0). It was deduced from these data that skin cancers occur more commonly in workers exposed to sunlight.

Data collected by Schrek showed the order of the most common location of epidermoid skin cancers to be the ears, hands and upper parts of the face, whereas the order of predilection for basal-cell cancer is the upper part of the face, the nose and the ears.[217]

British data have also shown a cancer predilection for those sites most exposed to light. It was found that 73.5 per cent of skin cancers among their agricultural cases occurred in the areas of the head, neck and face; the data accounted for 78.1 per cent among the miners and 69.7 per cent among the professional men. Among the agricultural workers the upper limbs were more frequently affected than the lower extremities; the reverse was true of the other occupational groups.

Schrek has noted that the predilection for skin cancer in those areas exposed to the sun does not hold true in Negroes, in whom the ratio is about equal between exposed and covered body surfaces.[218]

Numerous occupational exposures have been suspected of playing a role in the production of skin cancer. Among these is the classic chimney-sweep scrotal cancer. In 1923, Kennaway showed that the proportion of scrotal cancers to all cancer among the general male population was 1 to 600, whereas the proportion was 1 to 4 in chimney sweeps.[219] Scrotal cancer is also not uncommon among mule spinners. Among 64 fatal scrotal cancers recorded in England and Wales in 1923, 15 occurred in mule spinners. In 1946, Kennaway showed that the incidence of scrotal cancer in these two groups is still proportionally high. Among 723 scrotal cancers recorded in England and Wales from 1911 to 1940 were 415 cotton-mule spinners and 118 chimney sweeps. Next in frequency were gas, tar, pitch and creosote workers, accounting for 114 cases.[220] Lignite-tar cancers, occurring primarily in Germany, as well as those induced by coal tar and pitch, Scottish shale oil, petroleum, lubricating oils and aniline dyes, have been well summarized by Kennaway[220] and more recently by Henry.[221] Hueper lists the following agents as established carcinogens to the skin: anthracene (crude), arsenic, asphalt (artificial), burns (thermic), mineral oil (crude), oil shale, paraffin oil (crude), pitch, radioactive substances, roentgen rays, soot, spindle oil, tar and ultraviolet rays.[9] The fact that skin cancer may often occur in foundry workers has led Waniek to suspect heat as of etiologic significance.[222] Of great local interest is the Kangri cancer, observed among Indians who wear lighted charcoal braziers under their clothes and who frequently develop skin cancers in the lower-abdominal and inner-thigh regions.[223] Hesse was one of the first to describe skin cancer secondary to radiation. Fourteen years after the discovery of the x-ray he reported 95 cases of skin cancers, 50 of which occurred among physicians.[224]

The problem of arsenical skin cancers has been reviewed by Neubauer.[225] Hill and his associates, in an analysis of the data from a factory producing arsenic powder, showed that the incidence of cancer among the workers was significantly higher than among control cases and that the increase was primarily due to greater incidence of lung and skin cancers.[226] In a recent American study of a factory handling arsenic trioxide, no significant increase of cancer was noted among 146 deaths, which included 18 cancer deaths.[227]

In lip cancer, sunlight is believed to play the same role as in skin cancer in general. Willis wrote that "the great preponderance of tumors of the lower lip is explained as due to direct exposure of its mucocutaneous junction to sunlight, while the corresponding part of the upper lip is relatively shaded."[228] Pipe smoking is held to play a part in the production of lip cancer.[229] A recent statistical study by Levin and his associates has shown that the incidence of lip cancer is about twice as great among pipe smokers as among other smokers and nonsmokers.[49]

Experimental Data

In 1928, Findlay was the first to produce skin cancers in mice with a mercury arc.[230] Blum's studies have contributed much to the better understanding of the effect of ultraviolet light on the production of cancers of the skin. His work has established that wave lengths shorter than approximately 3200A are primarily responsible for the production of skin tumors. Experimental evidence with respect to coal-tar derivatives has been well reviewed by Greenstein and others.[17, 231, 232] The higher boiling-point fractions of petroleum have been shown to be carcinogenic to mice.[233] Potassium arsenate has been found to be weakly carcinogenic.[234]

Evaluation of Present Knowledge

The geographic distributions of the skin cancers, their anatomic site, the greater prevalence among those more exposed to sunlight and the greater incidence among fair-skinned people leave little doubt that sunlight plays an etiologic role in this form of malignant disease.

Certain occupations, as summarized above, are of added etiologic significance. The relation of pipe smoking to lip cancer is statistically established. There is no conclusive experimental or clinical evidence that heat *per se* can induce skin cancer.

Preventive Measures

Preventive measures chiefly concern the intelligent approach to sunlight exposure, a measure

that should apply especially to the fair-skinned peoples. Wide-brimmed hats should be advocated for those occupational groups in constant contact with the sunlight. Blum suggested avoidance of

> continuous year-around exposure to sunlight, particularly in the lower latitudes. Moreover, continuous regular exposure to artificial sources of ultraviolet radiation, even in moderate doses would seem unwise, particularly when used during the winter months, to supplement exposures during the summer either for "cosmetic" or "therapeutic" reasons. . . . protection can be gained from application to the skin of materials which absorb ultraviolet radiation. Among such agents, any which gives good protection against sunburn should be efficacious, but while many have been devised, not all are of great value.[235]

According to Blum, ointments containing titanium oxide as a scattering agent and phenylsalicylate as an ultraviolet absorbent are most effective.[235]

The industrial aspects of skin problems lie within the realm of improved personal hygiene, the greater use of closed production systems and the possible elimination of certain industrial procedures. In a recent article, the petroleum industry has shown how it has effectively approached the problem.[236] For scrotal cancer, good hygiene is of primary importance. In addition to the recommendations for protection against sunlight listed above, moderation in pipe smoking would reduce the incidence of lip cancer. Radiation of skin for nonmalignant disease should be avoided if possible.

Although the mortality of skin cancer is not great, its incidence makes it a significant problem. The application of prevention methods, especially through health education, may be a rewarding attempt.

Leukemia

Incidence

There is general agreement that an increase in the incidence of leukemia has taken place during the last decade. Sacks and Seeman, in reviewing the problem of apparent *versus* real increase in leukemia, concluded that the increase was probably real and could not be explained by an aging population or by improved diagnostic means.[237] The authors showed that the incidence of leukemia was 1.9 per 100,000 population in 1920 whereas it amounted to 3.7 in 1940. In 1948, deaths from leukemia accounted for 4333 males and 3115 females in the United States.[21] A mortality study made by the Metropolitan Life Insurance Company, comparing the mortality incidence from 1946 to 1947 to that of 1950 to 1951, showed an increase in deaths due to leukemia for both sexes.[23] Memorial Cancer Center data reported by Southam and his associates showed that admissions for leukemia among the total cancer admissions to the hospital accounted for 0.5 to 2.5 per cent for the period 1926 to 1946 but rose to 4.5 per cent in the period 1947 to 1948.[238] They suggested, however, that this type of increase could well be explained by increased general awareness of this disease, by its earlier and better diagnosis and by the realization that certain chemotherapeutic drugs might be of some help.

A study by Shimkin, Mettier and Bierman of 3 San Francisco hospitals showed a steady increase in incidence of myelogenous leukemia from 1910 to 1948. They stated, however, that it is impossible to conclude that this increase has been real. They observed a definite shift toward a higher proportion of females among myelogenous and other types of leukemia patients. The percentage of males in 517 cases of myelogenous leukemia up to 1950 was 57.4 per cent, whereas it was 53.3 per cent in 313 subsequent cases up to 1947.[239]

Suspected Etiologic Factors

Dameshek, in discussing the possibility of a real increase in leukemia, thought that such factors as radiation, benzol, benzol-ring drugs and arsenicals might be responsible for this increase. He emphasized that radiologists, photographers, dye workers and gardeners are susceptible groups.[240] Hueper regarded benzol, radioactive substances and roentgen rays as established carcinogens of blood-forming organs.[9]

Mallory, Gall and Brickley reviewed 12 cases of leukemia with chronic benzol exposure up to 1939.[241] According to a recent survey by Moeschlin, about 20 such cases are recorded in the literature.[242] Shimkin and his associates suggested that the increasing use of women in industries employing radiation and benzol might account for the higher proportion of females with leukemia found in their series today as compared to that of former years.

Radiation has been established as a factor in the production of leukemia. March, taking the period from 1927 to 1948, found that among 65,922 nonradiologist physicians who died, 0.51 per cent died of leukemia whereas among 299 radiologists who died during the same time period 4.58 per cent died of leukemia.[243] Radiologists thus have 9 times the expected incidence of leukemia, a figure verified by Uhlrich's study on similar data.[244] It was found that the incidence of leukemia in physicians as a whole is twice that of the general population; however, deletion of the radiologists from the group makes this difference slight.

Brues estimated that some Japanese survivors of the atom bomb were exposed to over 200r of total body irradiation.[245] Dunham, writing about the incidence of leukemia in the populations of Hiroshima and Nagasaki, recently stated that "among those within 1,500 metres of the hypocenter, there appears to be a ten-fold increase in the incidence of leukemia."[246]

Radioactive phosphorus has also been suspected of inducing leukemia,[247] but Brues considers present evidence inconclusive.[245]

Large-scale statistical studies, with the exception of those on the apparent effect of roentgen rays, remain to be made.

Experimental Evidence

Experimental evidence has recently been reviewed by Furth[248] and by Kirschbaum.[249] Leukemia has been induced in mice through exposure to irradiation.[250, 251]

Lignac obtained a higher incidence of leukemia and leukemia-like disorders (by injecting mice with benzol) than in controls but did not use inbred strains of mice.[252] Morton and Mider found no significant results with benzol in a well controlled experiment.[253]

Evaluation of Present Knowledge

With the exception of the data on radiation and possibly on benzol, no good evidence is at hand. Perhaps improved history taking and recording may yield new clues.

In evaluating leukemia data we must divide the material not only into acute and chronic cases but also into those arising at the different age levels, especially in the very young. Although leukemia in the young may be related to exogenous factors, it may also be concerned with intrauterine ones. If factors affecting the mother during pregnancy are of importance, they have failed so far to manifest themselves as such.

Preventive Aspects

Preventive aspects of leukemia, as they are apparent today, chiefly concern those workers exposed to radiation; among these, physicians rank foremost. Preventive measures will be outlined in a subsequent section on "Radiation."

Workers involved with benzol and its derivatives should observe every precaution. In general, industrial measures so far advanced are in line with those previously discussed.

Carcinoma of the Thyroid Gland

Thyroid cancer accounted for 0.3 per cent of male and 0.5 per cent of female cancer deaths in the United States in 1948.[21] According to data collected by Berard in 1924, the death rate of thyroid cancers in endemic goiter areas varied from 2.5 per cent to 4 per cent.[254] Furthermore, cancer of the thyroid gland is today somewhat more common in areas of endemic goiter than in those having none, but this is not as striking as it apparently was in former years. Many of the so-called endemic goiter areas in this country have largely disappeared. Crile writes in this regard:

> In the past the Great Lakes area has been one in which goiter was to some degree endemic, but I think with modern transportation, the increasing use of frozen and canned foods which come from all over the country and the iodinization of salt, that there is very little endemic goiter in this area among the young and middle-aged people. We certainly do not see the large goiters that we did 20 years ago.[255]

The state of Michigan had an incidence of goiter of 38.6 per 100,000 in 1924, whereas in 1950 four counties in Michigan in which iodized salt had been used for twenty-five years had an incidence of only 1.4.[256] Kimbal states that although good statistical data on cancer of the thyroid gland in these areas is not available at present "there can be no doubt at all but what iodized salt had practically eliminated goiter and adenoma of the thyroid among school children where it has been used for the past 25 years."[256]

A decrease in goiter and thyroid cancer has also been noted in animals. Ivy found that 98 per cent of his dogs autopsied between 1918 and 1925 had goiter and 1.6 per cent had apparent thyroid cancer with gross pulmonary spread.

Since 1925, one or two years after the introduction of iodized salt into the Chicago area, the incidence of goiter and thyroid cancer almost completely disappeared in dogs.[257]

Recent data from Switzerland, made available through the kind co-operation of Schinz, seem to confirm Kimbal's data. The frequency of goiter among newborns has decreased since the use of iodized salt.[258] A great decrease of goiter has also been noted among Swiss army personnel.[259] Iodized salt was first introduced in Switzerland in 1922. Complete data on the use of iodized salt and on the death rate of thyroid cancer from the canton of Zurich are of great interest. In this canton iodized salt was first introduced in 1923, at which time 18 per cent of the salt used was iodized. This percentage amounted to 13 per cent in 1930, 53 per cent in 1936, 55 per cent in 1940, 70 per cent in 1946 and 95 per cent in 1950.[260] The incidence data for death from cancer of the thyroid gland per 100,000 in the canton of Zurich for males and females were as follows: 1906-1915, 2.04 and 1.43; 1916-1925, 2.12 and 1.59; 1926-1935, 1.40 and 1.74; 1936-1945, 0.65 and 0.94.[258] A marked drop in the death rate from thyroid cancer, particularly since 1936, is evident and has led Schinz to conclude that "prophylaxis of goiter is a prophylaxis of cancer of the thyroid."[261]

Nutrition is generally considered one of the factors accounting for the greater incidence of goiter in certain areas, a factor that seems to depend on the relative potency of goitrogens and antigoitrogens in our food. The relation of nutrition to goiter has recently been reviewed by Greer.[262] It has been shown that certain foods, particularly those belonging to the cabbage family, — and among these especially rutabaga and, to a lesser extent, turnips,— contain an active antithyroid principle.[263] These findings are based not only on animal data but also on verified studies in man. The incidence of simple goiter increased in Belgium from 19 to 29 per cent, comparing the period 1936-1939 to 1941-1945.[264] This was thought to be due to the greater consumption of cabbage and kohlrabi during the latter time-period. Himsworth reported a high incidence of goiter among monks who were forced to live on

a diet of rutabaga and turnip bulbs.[265] However, this finding did not hold uniformly true for all persons who had to live primarily on vegetable diets during the war.

The iodine content of the diet may have played some role in this regard. Animal experiments have shown that iodine can at least partially inhibit the effects of goitrogenic diets. The role of iodine in the possible prevention of goiter is well accepted. The data from Michigan and Switzerland previously cited give good evidence in this respect.

In addition to nutritional factors, several therapeutic agents have been incriminated in the etiology of cancer of the thyroid gland; among these thiouracil and radioactive iodine predominate.

Thiouracil has been shown to induce thyroid adenomas and carcinomas in the experimental animal.[266, 267] Money and Rawson showed that the effect of thiouracil can be enhanced by injecting dibenzanthracene into the animals.[268] Recently, Morris and Green have found that by transplanting thyroid glands of rats fed on thiouracil to rats also being given thiouracil and thus exposing them over a longer period of time to the action of a goitrogen they could induce autonomous thyroid tumors.[269] There is no evidence in human beings that thyroid cancers have been caused by the clinical use of thiouracil since its introduction about a decade ago.

Gorbman, by giving large dosages of radiation iodine to mice, obtained pituitary tumors,[270] which have been shown by Goldberg and Chaikoff to be on the basis of hypothyroidism leading to a benign hypertrophy and hyperplasia of the basophilic cells of the anterior pituitary lobe.[271] Goldberg and Chaikoff studied 10 rats killed at eighteen months after having received a single dose of radioactive iodine and found that 2 animals had multiple adenomas as well as anaplastic nonencapsulated neoplasms of the thyroid.[272, 273] As far as the human use of radioactive iodine is concerned, no malignant effects have so far been recorded, but since it has been in use only a few years it is too early to make conclusive statements. In general, it is thought, as expressed by Rawson and his group, that the use of radioactive iodine should be restricted to persons over forty-five years of age or used in younger patients only if other forms of therapy are contraindicated.[274]

A possible relation between thymus irradiation and the development of thyroid cancers in children has been reported by Duffy and Fitzgerald.[275] Out of 28 children with thyroid cancer, 10 had received previous irradiation for hypertrophy of the thymus gland. According to Rawson, this ratio has been maintained in subsequent cases.[274]

Among preventive measures against thyroid cancer, those concerning nutritional factors seem to be the most outstanding, especially if the concept is held that hyperplasia of the thyroid gland may lead to neoplasia. Goitrogenic diets may be of some significance in this regard.

Data on both animals and human beings indicate that iodine supplements to the diet are one factor that may lower the incidence of goiter as well as of thyroid cancer. Since iodine supplements can be given without difficulty, efforts should be made to ensure adequate intake in all population groups. Possible relations of nutritional factors to thyroid cancer depend largely on the assumption that thyroid neoplasms, benign and malignant, occur as an end result of hyperplasia. Even if only a small number of thyroid cancers can be affected, prophylactic nutritional therapy, as suggested, appears indicated.

Carcinoma of the Breast and Endometrium

Two exogenous factors have been shown to play a role in the induction of breast cancer — the milk factor and administered estrogens.

Bittner[276] and his group were the first to demonstrate that a milk factor was of significance in the production of breast cancers in mice, a subject reviewed by Porter and Thompson[277] and by Berner.[278] Particles of the size of viruses have also been demonstrated in human breast milk and have been found to be more prevalent in breast milk of breast-cancer patients, even though they are also found in the milk of patients without breast cancer.[279, 280] Clinically, in contrast to animal experiments, no significant correlation between breast feeding and the incidence of breast cancer has been established. Adair found that as many women among his control group had been breast fed as among his breast-cancer patients.[281] In a statistical evaluation of 88 breast-cancer and 86 control patients, Horne could find no significant difference in respect to history of breast feeding between the two groups. He was careful to record even a single breast feeding, since a single exposure to breast feeding has been shown to transmit the milk factor in mice.[282]

Since the classic experiments of Loeb and of Lacassagne, estrogens have been regarded as of major importance in the etiology of breast cancer.[283, 284] Clinical evidence, however, has been much less clear cut. In 1941, Auchincloss and Haagensen reported a case of breast cancer that they thought could have been induced by estradiol benzoate. It occurred in a patient who had received 79 mg. of estradiol benzoate over a two-year period.[285] Although several other suggestive cases have been reported, no large-scale data have been recorded incriminating estrogen therapy in the production of breast cancer in human beings.[286] The participants in the 1949 Panel Discussion of the National Cancer Society concluded that there was no worth-while evidence that estrogens are a significant factor in the production of human breast cancer.[287]

Estrogens are also suspected of playing a role in the production of breast cancer in males. The first case was reported in 1948 in a male patient with prostate cancer who had received 1097 mg. of diethylstilbestrol over 489 days.[288] So far, 12 cases have been recorded in the literature, a subject recently reviewed by Campbell and Cummins.[289] These authors presented a case of cancer of the breast in a man treated with diethylstilbestrol for cancer of the prostate. Through a special staining technic they showed the breast lesion to be metastatic cancer of the prostate. They suggested that if the other reported breast cancers had been similarly examined they might also have been shown to be metastatic from the prostate.

Gynecomastia but not breast cancer has been reported in male workers handling stilbestrol.[290]

In contrast to breast cancer, human evidence is more suggestive than experimental data that estrogens are of some significance in the induction of endometrial cancer. Although experimental work in mice, rabbits and monkeys showed by and large only hyperplastic endometrial changes, several human cases have been reported suggesting that estrogens are of etiologic significance. The first case was reported in 1946 in a forty-three-year-old woman who had received estrogenic substances almost continuously for eight years. She received 392 mg. of estradiol as benzoate or dipropionate, 1085 mg. of estrone sulfate and 18 mg. of diethylstilbestrol. In this patient the vaginal smear showed atrophy after withdrawal of estrogens.[286] Speert found, among 56 cases of endometrial cancer, 12.5 per cent with a history of estrogen therapy for varying lengths of time prior to admission. Four of these patients had been treated with estrogens for over two years. Speert believed that less than 12.5 per cent of the general population is under continuous estrogen therapy and suggested that estrogens have a carcinogenic effect on the human endometrium.[291] So far, more than 20 endometrial cancers have been recorded in whose induction estrogens were believed to have played a role.[292]

Radiation is also suspected of playing a role in the production of endometrial carcinoma. Among 270 patients with uterine cancer, collected by Speert and Peightal, 8 per cent had received pelvic irradiation for benign conditions from eight months to nineteen years prior to the clinical development of the endometrial cancers, whereas only 0.3 per cent of patients with cervical cancers gave such a history.[293] Corscaden and Gusberg[294] followed 1100 women who had received radium therapy for benign pelvic disease for 6.7 years and found 9 cases of cancer of the uterus and 6 of the cervix. They concluded that the number of uterine cancers is 3 times that expected from the general female population.[292] Crossen and Crossen found 4 endometrial cancers among 526 patients with myomas of the uterus previously treated with irradiation, compared to 37 endometrial cancers among 2136 patients with myomas of the uterus not so treated with irradiation, thus finding no significant difference in the incidence of endometrial cancer between the two groups.[295] Smith and Bowden found that 39 among 808 patients with histologically proved endometrial cancers had been previously irradiated but that only 8 of these patients both had been asymptomatic for an interval of ten or more years since the irradiation and had originally had a confirmed negative biopsy. Under such stringent criteria and since proper control data were not available, these authors concluded that "it is impossible, at this time, to state whether irradiation for benign uterine lesions induces uterine cancer."[296] Further data are needed for definitive evaluation of the effect of irradiation in the development of endometrial cancers.

Data on estrogens suggest that prolonged and excessive estrogen therapy may play a role in the induction of some endometrial cancers and in that of an occasional breast cancer. It cannot be decided whether such activity is based on the hormone's ability to activate already present cancer cells or whether administered estrogens are *per se* carcinogenic to human beings.

In commenting on animal data, Novak wrote that "the dosages of estrogen required to reproduce cancer in animals have been huge, far larger and more prolonged when related to the human scale than anyone would ever employ for therapeutic purposes."[297] Lamar emphasized, furthermore, that the animal results have been obtained primarily in highly susceptible strains.[298] Druckrey concluded: "On the basis of my experimental work, estrogens should not be regarded as true carcinogens. They have only a co-carcinogenic action through the fact that as a 'Proliferations Substanz' they can further the development of a neoplasm from cancer cells already present."[202]

Gardner suggested that "for practical purposes, it might be well to consider them as possibly carcinogenic when administered continuously, although the investigators in the field may find increasing evidence to doubt their direct participation in malignant transformations of body tissues."[299] Nathanson took a similar stand.[300]

As far as cancer prevention is concerned, this problem is academic. The proper use of such hormones, however, is of practical importance. In spite of the fact that estrogens given therapeutically may be responsible for only a few genital cancers, one should caution against their unnecessary and unchecked use.

Novak recently stated that "we should try to avoid estrogen therapy or at least hold it down to minimum proportions in women with a very strong family history of cancer, those who suffer with

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any so-called precancerous lesions and those who have previously been treated for cancer whether surgically or radiologically."[301]

These recommendations appear worth following. A prolonged and excessive use of estrogens should be avoided, if merely for the reason that a benign condition rarely warrants such extensive therapy. It should also be emphasized that estrogen therapy should not be given unless the patient has had a complete physical check-up, including pelvis and breast examination. Even though human evidence on the carcinogenic effects of estrogens is still debated, cautious use of these hormones is strongly urged.

Radiation

The possible role of radiation effects in respect to lung cancer, leukemia and thyroid, endometrial and skin cancers has been discussed. Some other facts remain to be considered. The role of radiation in human carcinogenesis has recently been well reviewed by Brues.[345]

Sarcomas

In 1931 Martland presented 10 cases of osteogenic sarcoma that developed seven to twelve years after the ingestion of radium dial paint among watch-dial painters.[302] Cahan and his co-workers summarized the data on the relation between osteogenic sarcoma and radiation, presenting 14 cases from the literature to which they added 5 of their own. The latency period between radiation and tumor development of their cases was 11.2 years.[303] Recently, a case of osteogenic sarcoma of the lumbar vertebras following million-volt "prophylactic" therapy for a seminoma of the testis following orchiectomy was reported.[304] More than 4400 r were given, which was considered in excess of the calculated lethal dose for this type of tumor, which is estimated to lie between 2000 and 2400 r.

Spitz and Higinbotham urged that the possibility of osteogenic sarcomas be considered before giving too high a dosage of x-ray, especially if given prophylactically.[304]

A recent report described extraskeletal osteogenic sarcoma following an irradiation of 4000 r given in 10 exposures over seventy days. This tumor arose just beneath the irradiated skin four years after therapy.[305]

Experimental work concerning bone-tumor formation following irradiation has been reviewed by Hatcher[306] and by Cahan and his associates.[303]

Atomic Energy

Knowlton, reporting from Los Alamos, found a small but significant drop in the neutrophil and lymphocyte counts in workers who had been exposed to about 0.2 r per week for two years.[307]

After the use of the atomic bomb, Japanese survivors were carefully followed for the appearance of blood disorders. Warren reported a decided drop in the white-cell count of many survivors.[308] The subsequent rise in the incidence of leukemia among these survivors has been previously cited.[246]

Preventive Measures

Protective measures against radiation hazards should be of primary concern to all exposed to radiation. Such measures have been outlined by Mayneord[309] and by Morgan.[310] The maximum values of radiation exposure as recommended by the last International Radiologic Congress should be observed.[311] This applies not only to those who constantly work with radiation and equipment but also to those who use such equipment only at irregular intervals. The full-time radiologist, familiar with protective devices and aware of the possible dangers of radiation exposure, may indeed have less exposure than the physician who occasionally but unwisely uses radiation equipment. It is recommended that all persons using radiation apparatus carry a photographic film monitor at all times, to be checked at weekly intervals. In addition to this, periodic blood counts are indicated for those having a more constant exposure.

In radiation therapy, preventive measures apply also to the wise choice of dosage, which should never be higher than necessary. The possible dangers of low-voltage x-rays should be appreciated and should be avoided in the use of nonmalignant lesions.

Of greatest importance, as far as preventive measures are concerned, however, appear the precautionary measures of those persons exposed to radiation in their field of work. Properly constructed rooms and storage places and proper gowns and gloves are preventive measures, of course, but none of these can replace constant vigilance of the workers themselves. Proper precautionary measures have saved and may continue to save many lives among radiation workers, among which physicians comprise a large group.

Summary

Future Clinical Studies

It is hoped that this communication may give fresh impetus to clinical investigations in environmental cancer. As may be seen from the data presented, much work remains to be done. A considerable portion of the data shown, although suggestive, are difficult to evaluate properly because adequate controls are lacking.

Environmental cancer studies must be specifically planned and carried out by personnel interested in and trained for such investigation. The studies must concern themselves with all possible etiologic factors for any given type of lesion. Only thus may sound conclusions be drawn. After the proper questionnaires have been prepared, the survey

must be carried out on a statistically sufficient number of patients and must in all cases have an adequate number of control patients, who should be of the same age and economic and racial distribution as the patients with cancer. Since any given hospital may not have enough cancer patients to be studied, close co-operation of several hospitals may be required. It will be advantageous if the data can be collected from several different sections of the country, in order to eliminate possible local factors. Should such investigations be planned on an adequate scale and carried out, — if possible on a worldwide basis, — much additional information about the causation of cancer will be discovered.

Table 1. *Etiologic Factors and Preventive Measures in Cancer.*

Site of Cancer	Suspected Environmental Carcinogenic Agents	Preventive Measures
Lung	Tobacco,* chromate,* radioactive dust,* arsenic,† lubricating oils,† isopropyl oils,† metal dust and fumes,† paint,† wood dust,† nickel,† asbestos†	Moderation of smoking habits Research into possible carcinogenic fractions of tobacco tars with the aim of their possible removal or reduction Industrial hygienic measures§
Larynx	Tobacco,† alcohol,‡ metal dusts and fumes‡	Possible moderation of tobacco habits indicated (definite preventive suggestions must await further environmental studies)
Penis	Smegma or other agents under the foreskin*	Circumcision in infancy Good genital hygiene
Cervix	Smegma or other agents under the foreskin of the penis,† therapeutic estrogens‡	Universal male circumcision seems indicated, but further investigation is needed before definite preventive measures can be recommended
Prostate	Smegma or other agents under the foreskin‡	
Bladder	Beta-naphthylamine,* bilharziasis,* benzidine†	Industrial hygienic measures§ Improvement of waterways and supplies
Oral cavity	Tobacco,* syphilis (tongue),* dietary deficiencies,† alcohol,‡ poor teeth,‡ oral sepsis‡	Moderation of tobacco habits Early treatment of syphilis Improved diets (especially vitamin A and B and complexes and proteins)
Esophagus	Tobacco,† alcohol,† dietary deficiencies,† thermal factors,‡ spices,‡ poor dental and oral hygiene‡	Moderation of tobacco habits Moderation in use of certain alcoholic beverages Improved diets (especially in northern Europe)
Stomach	Thermal factors,‡ spices,‡ alcohol,‡ tobacco,‡ poor dental and oral hygiene,‡ dietary factors‡	Present evidence too inconclusive to suggest definite preventive measures
Liver	Dietary deficiency,* alcohol,‡ butter yellow,† bilharziasis‡	Improved diets (especially in vitamin B complex and proteins) Omission of butter yellow as food-coloring agent
Skin	Ultraviolet light,* arsenic,* tars,* oils (mineral, shale and paraffin),* roentgen rays,* tobacco (pipe-lip)* anthracene,* asphalt,* pitch,* heat‡	Limited exposure to sunlight, especially of susceptible persons Use of good preventive ointments Industrial hygienic measures§ Cautious use of x-ray Moderation in pipe smoking
Leukemia	Radiation,* benzol*	Cautious use of and protection from x-rays Industrial hygienic measures§
Thyroid gland	Dietary factors,† radiation,† positive goitrogenic agents,† radioactive iodine‡	Adequate supplements of iodine to diets, if insufficient Irradiation of thymus gland in the young (to be carried out with caution) Radioactive iodine (to be avoided under the age of forty-five)
Breast	Milk factor,‡ therapeutic estrogens‡	Present evidence too inconclusive to suggest definite preventive measures
Endometrium	Therapeutic estrogens,‡ radiation‡	Cautious use of estrogens and of pelvic irradiation

*Evidence is good.
†Evidence is suggestive.
‡Evidence is inconclusive.
§Industrial hygienic measures include instruction in hygiene, good washing facilities, protective clothing, daily change of work clothing, rotation of personnel, closed production systems, good ventilation and periodic medical examinations.

Experimental Studies

In the field of environmental cancer, animal studies must take a secondary place. This belief holds true not only because of known species differences but also because many human exposures to exogenous agents are difficult, if not impossible, to duplicate in the laboratory animal.

This recommendation is not meant to deny the worth of animal experimentation. It is stated because there is a tendency to discount clinical findings because they cannot be verified in the experimental animal. In environmental cancer studies, human data must represent the most conclusive evidence. If such evidence can be confirmed, — as has been done, for instance, in the bladder tumors with B-naphthylamine dyes, — it strengthens the findings in human beings. Negative findings in the laboratory animal, however, should not rule out the etiologic significance of suspected carcinogenic agents in man.

The Role of Exogenous Factors

The majority of cancers in whose induction exogenous factors are believed to play a role are rare in animal species other than man. This observation, together with the fact that in most of these cancers exposures demonstrated in man do not exist in animals, seems to confirm the concept that exogenous factors play a significant role in the production of these cancers. This observation holds true, in particular, for the epidermoid types of cancer. The evidence at hand suggests that although epidermoid cancer may occur sponta-

neously it does not commonly do so. Induction appears generally to depend on some form of exogenous irritant. This belief does not deny the importance of factors of internal predisposition, which must exist since obviously not every person exposed to suspected carcinogens develops cancer. This concept also does not interfere with any present theories of the origin of cancer, any one of which it can supplement.

A Practical Approach

It has been the purpose of this communication to evaluate practical steps that can be taken to lower the incidence of certain types of cancer. It is recognized that many basic questions concerning the induction of cancer remain to be answered, but, — for the present at least, — these answers lie beyond our reach. For this reason, measures must be sought that can be comprehended and practiced now. The exogenous factors discussed are to be considered in this light. Their function and their significance may be understood although the mechanism of their induction may remain unknown. However, just as other disease processes have been coped with when not every mechanism of their induction was understood, so advantage must be taken of the existing knowledge of environmental cancers.

In the future the ever increasing knowledge of exogenous carcinogenic factors and their role in the causation of cancer may be of great value in unveiling the nature of cancer itself. Of foremost immediate and practical value, however, is the part they play in the prevention of human cancer today. The goal of cancer research, as in all other diseases, is prevention.

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MEDICAL INTELLIGENCE

ACTH AND CORTISONE IN THE TREATMENT OF SICKLE-CELL ANEMIA*

Report of a Case

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SICKLE-CELL anemia is a hereditary and familial form of chronic hemolytic anemia essentially peculiar to Negroes. Although many patients show a remarkable adaptation to their state of chronic anemia and live for many years, sickle-cell anemia is a serious malady with an ultimately fatal outcome. To date, treatment of this disease and its crises has been discouraging and unsatisfactory. The following case report describes the results obtained with prolonged treatment with ACTH and cortisone.

Case Report

On August 3, 1951, a 20-year-old dyspneic Negro woman entered the emergency room in marked distress, with the chief complaint of "sudden sharp agonizing pain" in her abdomen, associated with marked pains throughout both lower extremities, vertigo, weakness and chills. She denied any nausea, vomiting, diarrhea, constipation, tarry or bloody stools or hematemesis. There was no frequency, dysuria or hematuria.

Her history revealed that as a child she had suffered from persistent weakness, easy fatigability, frequent sore throats and frequent episodes of abdominal pains. At the age of 5, she was hospitalized at another institution. Examination at that time revealed the liver to be 2 fingerbreadths below the costal margin and the spleen to be at the level of the umbilicus. Laboratory findings revealed hemoglobins ranging between 46 and 64 per cent, red-cell counts between 2,280,000 and 2,960,000 and reticulocyte counts of between 14 and 43 per cent. Nucleated red corpuscles ranged from 3 to 29 per cent and the icteric index between 10 and 33. Sickling of the red cells was noted. The diagnosis of sickle-cell anemia was made. A splenectomy was performed.

Throughout the patient's life the disease was characterized by frequent occurrences of the familiar sickle-cell crises, which manifested themselves by precipitous lowering of the hemoglobin and red-cell counts and by such symptoms as fever, chills, malaise, severe bone and abdominal pains, nausea and vomiting and extreme prostration.

On a previous admission, laboratory results revealed a red-cell count of 2,830,000, with a hemoglobin of 58 per cent. Target cells, basophilic stippling and polychromatophilia were observed. A sedimentation rate was 1.5 mm. in 60 minutes; after oxygenation the same blood sample revealed a sedimentation rate of 45 mm. in 60 minutes. A sickle-cell preparation was strongly positive, with 90 per cent of the cells being sickled.

Physical examination revealed a dyspneic, thin woman in extreme distress. There was marked pallor of the skin and mucous membranes. Chest findings consisted of dry inspiratory and expiratory rales over the right base posteriorly and a pleural friction rub over the left anterior chest at the sixth intercostal space. The respiratory rate was 28. Cardiac findings revealed a tachycardia of 128, with a sinus arrhythmia, and a soft systolic apical murmur. The blood pressure was 104/68. There was generalized abdominal tenderness and increased costovertebral-angle tenderness on the left. Both knees were edematous and tender. Palpation of both tibias revealed diffuse tenderness throughout the length of these long bones and an area of swelling on the anterolateral aspect of the left lower leg.

A hemogram made on admission revealed a red-cell count of 2,430,000, a white-cell count of 23,650 with 58 per cent neutrophils, 36 per cent lymphocytes and 6 nucleated red cells. Urinalysis revealed ++++ proteinuria. Intravenous pyelograms and x-ray films of the abdomen were negative. X-ray examination of the chest revealed a slight thickening of the pleura on the right side at the costophrenic angle. The lungs were clear. An electrocardiogram showed a sinus tachycardia with a rate of 134. She was placed on bed rest; nasal oxygen; streptomycin, 500 mg. every eight hours; penicillin, 400,000 units every 12 hours; and the immediate administration of 1 pint of blood. Morphine sulfate, 1/4 gr., and atropine sulfate, 1/150 gr., were given every 4 hours. Toward evening, her temperature rose to 104.2°F., and increasing amounts of analgesics and sedatives were required.

Her clinical condition continued on a steady downhill course. The blood pressure was 92/60. The temperature fluctuated at 104°F. in spite of antipyretic and antibiotic therapy. By the 8th hospital day she had received 4 blood transfusions. She developed marked epistaxis. Her immediate prognosis was grave. The red-cell count was 1,810,000,

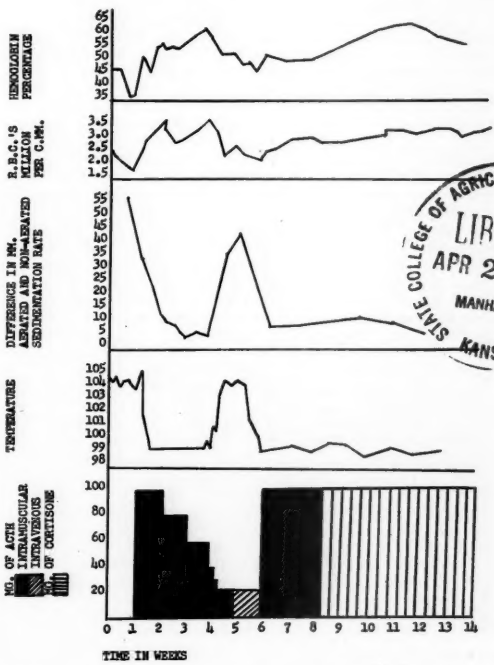
HEMOGLOBIN PERCENTAGE
R.B.C.'S MILLION PER C.MM.
DIFFERENCE IN MM. AERATED AND NON-AERATED SEDIMENTATION RATE
TEMPERATURE
NO. OF ACTH INTRAMUSCULAR INTRAVENOUS OF CORTISONE
TIME IN WEEKS

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FIGURE 1. *Chart Showing Clinical and Laboratory Response to ACTH and Cortisone.*

The intravenous ACTH was given in 1000 cc. of 5 per cent glucose in water and allowed to run over an eight-hour period. Sedimentation rates were determined from blood obtained after venous stasis for six minutes.

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with a hemoglobin of 35 per cent. The difference in aerated and nonaerated sedimentation rates was 54 mm. in one hour (Fig. 1). X-ray films revealed bone infarcts involving the left tibia, near the knee joint, and both tibias near the ankle and irregular calcification with cortical thickening. These were consistent with the diagnosis of sickle-cell anemia. A Thorn test revealed an adequate drop in the circulating eosinophil response. She was started on 25 mg. of ACTH intramuscularly every 6 hours (Fig. 1).

On the 9th hospital day the clinical response was dramatic. Within 24 hours after the institution of ACTH therapy the patient was sitting up in bed. Her temperature and pulse dropped to normal. She had very few complaints. On the following days she continued her dramatic asymptomatic uphill course. She was up and about and appeared well. A reduction in the dosage of ACTH was ordered.

As is shown in Fig. 1, this reduction in dosage was apparently carried out too rapidly. On the 35th hospital day she began to complain of right-upper-back pain, a harsh productive cough and hemoptysis. Chest findings revealed impaired resonance and depressed breath sounds in the right chest posteriorly. Her temperature began to rise. The difference in aerated and nonaerated sedimentation rates rose to 42 mm. Posteroanterior and lateral views of the chest revealed an area of consolidation in the right lower lobe, with pleural effusion and probable lung abscess, consistent with pulmonary infarction. (Chest films made six days previously had revealed clear lung fields.) Thus, another crisis had occurred, but this was complicated by a suppurative lung involvement. Adequate dosage of ACTH was resumed. Except for a productive cough associated with some right-chest pain, she again began a dramatic uphill course.

On the 60th hospital day ACTH was discontinued, and 50 mg. of cortisone every 12 hours was started. She continued her excellent response, was afebrile and was up and about. The difference in her aerated and nonaerated sedimentation rates was only 7 mm. (Fig. 1). To facilitate resolution of the lung involvement, a right-phrenic crush was performed, with excellent results.

On the 97th hospital day the patient was discharged on a maintenance cortisone dosage of 50 mg. every 12 hours. After discharge, the patient was completely asymptomatic. There were no episodes of weakness or fatigue. Her appetite improved, and she gained 4 pounds. Three weeks after discharge it was decided to reduce her cortisone to one-half dosage. This reduction was followed 2 days later by the onset of thrombophlebitis, and she was again hospitalized. The cortisone dosage was elevated to 100 mg. per day, and she was placed on Dicumarol for 6 days. She again displayed an amazingly rapid response and was discharged 6 days after admission. At present she is on 100 mg. of cortisone per day. She is well, gainfully employed and completely asymptomatic.

Summary and Conclusion

ACTH and cortisone have produced a dramatic clinical improvement with complete regression of symptoms in a case of sickle-cell anemia.

It has been demonstrated that there is a definite relation between the dosage of the hormones used and the difference in aerated and nonaerated sedimentation rates, a diagnostically significant test for sickle-cell anemia. It has also been shown that by lowering the optimum dosage of these hormones after complete regression of symptoms another sickle-cell crisis was allowed to manifest itself by a precipitous fall in the percentage of hemoglobin and a fall in the red-cell count and by such severe constitutional symptoms as marked fever, chills, chest and extremity pain and the development of a pulmonary infarction. On reinstitution of adequate dosages of ACTH, followed by cortisone maintenance, the patient again demonstrated an adequate and dramatic response.

Apparently the use of these hormones does not significantly elevate the red-cell count or the percentage of hemoglobin, although marked lowering of the dosage was associated with a reduction in both these levels.

Although some observers would be of the opinion that the disease would fall into the category of probable contraindications to ACTH and cortisone therapy because of recent studies indicating the increasing frequency of thromboembolic phenomena occurring on this therapy, it appears that this method of treatment in some manner prevents the vascular occlusions commonly associated with this condition.

It is concluded that ACTH and cortisone have a definite place in the treatment of sickle-cell anemia and crisis.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38151

PRESENTATION OF CASE

A sixty-eight-year-old white housewife was admitted to the hospital because of diffuse skin rash.

For about five years prior to admission she had had periodic attacks of arthritis, for which, three months before admission, she had been treated for two weeks with corticosorbate. During the second week of treatment she developed swelling of the eyelids and a few days later an erythematous rash over her chest and back. The drug was discontinued, but the rash remained unchanged; hence she was given Cortone, 75 mg. a day. Since there was no improvement on this therapy, it was stopped after two weeks. Following the withdrawal of the drug the rash became more marked and spread to involve the face, neck, chest, arms and hands. The only other medicine taken was aspirin. The rash was red and scaly, was not vesicular and did not itch. Two weeks before entry she began to notice pain in her mouth on mastication and also some dysphagia; the latter was most noticeable when she swallowed fluids. For a few weeks prior to entry she had pain in the shoulder, elbow and neck and, a few days prior to entry, pain in the right hip; the pain in these joints was accentuated by movement.

Her general condition was poor, and she believed she had lost a substantial amount of weight. For the few weeks before admission she had eaten very little because she felt that she was "unable to digest her food." For four days prior to entry she had had fairly marked dyspnea, present at rest. There had been no cough, chest pain, swelling of the ankles or vomiting.

Physical examination revealed an obese, well developed woman. There was periorbital edema, diffuse seborrhea of the scalp and a diffuse purplish-red scaling mottled erythematous rash of the face, neck, shoulders, arms and forearms. There was marked redness with swelling and scarring of the buccal mucosa and the soft palate. The tongue was irregularly mottled with some areas of scarring. There was a soft blowing Grade II systolic murmur. The lungs, abdomen and lower extremities were not remarkable.

The temperature was 100°F., the pulse 124 and the respirations 24. The blood pressure was 158 systolic, 78 diastolic.

Examination of the blood showed a hemoglobin of 13.5 gm. and a white-cell count of 7150, with a normal differential. The erythrocyte sedimentation rate was 0.9 mm. per minute (corrected). The nonprotein nitrogen was 22 mg., the fasting blood sugar 106 mg., the bilirubin 0.4 mg. direct and 0.7 mg. total, the total protein 5.4 gm., the albumin 3.12 gm., the globulin 2.28 gm., the calcium 7.9 mg., the phosphorus 3.8 mg. and the phosphatase 7.2 units per 100 cc. The serum sodium was 127.5 milliequiv., the potassium 5.9 milliequiv., the chloride 98 milliequiv. and the carbon dioxide 98 milliequiv. per liter. Blood cultures were negative. The urine had a specific gravity of 1.018 and was normal. Examination of the urine was negative for uroporphyrins. Roentgenograms of the chest showed a prominent left ventricle, a tortuous aorta and numerous linear shadows in the lower half of each lung field. X-ray films of the hands showed slight decalcification with considerable deformity and narrowing of the interphalangeal joints with varying degrees of degenerative changes about the margins. X-ray films of the knees showed narrowing of the joint spaces and marked degenerative changes. An electrocardiogram showed a normal sinus rhythm with a PR interval of 0.16 second, a QRS interval of 0.07 second, normal voltage and left-axis deviation. The T waves were upright in Leads 1, 2, AVL, V_2, V_3, V_4, V_5 and V_6, inverted in Lead 3 and diphasic in Lead AVF. No lupus erythematosus cells were found on a special lupus-erythematosus-preparation blood smear.

Shortly after admission the patient developed rather marked brawny edema of the left forearm and hand; pulsations in both arms were equal and good. The decholin circulation time, left wrist to tongue, was 16 seconds. She continued to have a low-grade fever, up to 100°F., and a fast pulse rate. She had a few inspiratory rales at each lung base but no dilatation of the neck veins and no edema in the lower extremities. She had exacerbations and remissions of the diffuse skin rash, often with vesiculation, and of the edema in the face and upper extremities. The lesions of the mouth and tongue did not improve, became ulcerated and caused much difficulty in swallowing both fluids and solids. After a few weeks in the hospital she began having episodes of disorientation. On the twenty-first day the prothrombin time was 18 seconds (normal, 15 seconds), the thymol turbidity 5.5 units per 100 cc., the cephalin flocculation ++ in 24 and 48 hours and the sedimentation rate 1.9 mm. per minute. In the seventh week of hospitalization she developed diffuse myasthenia, most prominent

in the shoulder, thigh and neck muscles; she had some difficulty in swallowing but no ptosis or diplopia. The weakness progressed, and she was unable to hold up her head or lift her arms; there was little or no weakness in the hands and only slight weakness in the thighs. The muscles were not tender, and atrophy was not apparent. The triceps and abdominal reflexes were absent. A smooth, firm, nontender liver was palpable 2 to 3 fingerbreadths below the costal margin. The sedimentation rate was 0.1 mm. per minute and the prothrombin time 16 seconds (normal, 15 seconds). The hemoglobin was 9.3 gm., the total protein 6.24 gm., the albumin 2.18 gm., the globulin 4.06 gm., the bilirubin 0.7 mg. total, the calcium 8.1 mg., the phosphorus 3.0 mg., the alkaline phosphatase 13.6 units and the nonprotein nitrogen 17 mg. per 100 cc. The potassium was 3.8 milliequiv. per liter. A cephalin-flocculation test was +++ in 24 and 48 hours and a bromsulfalein test showed 43 per cent retention in the serum. A two-hour specimen for urine urobilinogen contained 1.9 Ehrlich units. A twenty-four-hour urine specimen contained 0.94 mg. per pound of creatine and 4.0 mg. per pound of creatinine (weight, 140 pounds). A Coombs test was negative. An electrocardiogram showed nonspecific ST-segment and T-wave changes. On barium-swallow examination the transit of the barium through the esophagus was very slow.

Her course was progressively downhill with minor remissions. The hemoglobin remained in the neighborhood of 8 gm. despite transfusions. The prothrombin time dropped to 20 seconds (normal, 15 seconds), the cephalin flocculation was ++++ in 24 and 48 hours, the bromsulfalein showed 32 per cent retention in the serum and the total protein and albumin-globulin ratio remained at the previous level. She developed several episodes of atelectasis and pulmonary infection that were controlled by antibiotic therapy. One day during the fifth month of hospitalization, the temperature suddenly rose to 105.6°F. and the blood pressure dropped to 70 systolic, 40 diastolic; she rapidly became unresponsive and died four hours later.

Differential Diagnosis

Dr. Walter F. Lever*: At the time of admission this elderly woman, who had had mild rheumatoid arthritis for about five years, had a nonpruritic purplish-red scaling eruption on face, neck, chest, back, arms and hands of three months' duration. There was edema of the eyelids. There were oral lesions and dysphagia. She had pains in her shoulders, elbows, neck and right hip. Her general condition was poor.

At this stage two diagnoses stand out above all others; systemic lupus erythematosus and dermatomyositis. I would not be willing to decide at this stage which of the two diseases she had, although the extent of the cutaneous lesions and the presence of dysphagia would favor dermatomyositis. Joint pains are common in systemic lupus erythematosus and rare in dermatomyositis, but it is possible that the pains referred to as joint pains were located largely in the muscles and tendons rather than in the joint capsules.

Laboratory data obtained at the time of admission favor the diagnosis of dermatomyositis over lupus erythematosus. There was absence of leukopenia; there was no increase in globulin, which in systemic lupus erythematosus usually rises quite early in the course of the disease; the urine showed no abnormal findings; and no lupus-erythematosus cells were present. The radiograms of the hands and knees showed evidence of the old rheumatoid arthritis, which I believe was not immediately related to the disease process from which the patient was suffering. The electrocardiographic deviations were slight and nonspecific. Of interest is the low value for serum sodium in the presence of a slightly elevated value for potassium — a possible indication of adrenal insufficiency.

After admission the disease became gradually worse: Brawny edema of the left forearm and hand developed; the cutaneous eruption spread, became vesicular in places and was associated with edema of the face and upper extremities; the oral lesions became more severe; and the sedimentation rate rose to the very high value of 1.9 mm. per minute. All these manifestations may occur in dermatomyositis as well as in systemic lupus erythematosus. But then profound muscular weakness set in, so that the patient was unable to hold up her head or to lift her arm. That is strongly in favor of dermatomyositis. As is characteristic of dermatomyositis, the muscles were weak and not tender. The triceps and abdominal reflexes were absent. It is somewhat surprising that with such profound muscular involvement this patient did not show a higher excretion of creatine in the urine; the excretion of creatine in the urine per twenty-four hours was 128 mg. Although this value certainly is higher than one would expect in a woman past the menopause, it is lower than is generally observed in patients with extensive active dermatomyositis. The creatinuria occurring in dermatomyositis as well as in other diseases of skeletal muscle is at present thought to be due to the failure of diseased muscle to metabolize creatine into phosphocreatine, whereafter it is excreted in the urine as creatinine.† Thus, in diseases affecting muscles large amounts of creatine are excreted in the urine, often 300 or even 500 mg. per twenty-four hours.

There was evidence of damage to the liver, which I presume was nonspecific and due to the chronic illness of the patient. The bromsulfalein test showed

*Assistant dermatologist, Massachusetts General Hospital.

†Roche, M., Benedict, J. D., Yü, T. F., Bien, E. J., and Stetten, De W., Jr. Origin of urinary creatine in progressive muscular dystrophy. *Metabolism* 1:13-19, 1952.

43 per cent retention in the serum, whereas normally there is less than 5 per cent retention. Furthermore, a two-hour specimen for urine urobilinogen contained 1.9 Ehrlich units, whereas normally not more than 1.2 Ehrlich units is present. On the other hand, the positive cephalin-flocculation test cannot solely be ascribed to damage to the liver but may be the result of the rise in gamma globulin, indicated by the presence of 4 gm. of globulin in the serum by the sodium-sulfate fractionation method.

The patient died of her disease after a total duration of seven months. I believe she died of dermatomyositis. Weakness of her respiratory muscles, suggested by episodes of atelectasis, was probably a decisive factor in causing her death.

The autopsy showed, I suppose, extensive degeneration and inflammation of the skeletal musculature. Although the same process is observed in lupus erythematosus, it is, as a rule, much more severe in dermatomyositis. The heart muscle may also be involved in both diseases, usually more severely in dermatomyositis.

The histologic picture of the cutaneous lesions of dermatomyositis is usually indistinguishable from lupus erythematosus. In both diseases one observes atrophy of the epidermis with hydropic degeneration of the basal-cell layer. The degeneration of the basal cells may lead to detachment of the epidermis and thus to vesiculation. The corium shows edema with varying degrees of degeneration in the collagenous fibers.

The main difference between dermatomyositis and lupus erythematosus, aside from the difference in the severity of the muscular lesions, lies in the visceral lesions. Whereas systemic lupus erythematosus usually shows fairly distinct visceral lesions such as periarterial fibrosis in the spleen, focal necrosis in the lymph nodes, glomerulitis and endocarditis, such lesions are absent in dermatomyositis. Polyserositis, common in lupus erythematosus, is only rarely observed in dermatomyositis.

The lungs undoubtedly showed patchy bronchopneumonia, with pulmonary edema and areas of atelectasis.

The liver, I suppose, showed parenchymatous degeneration and fatty infiltration, which are secondary manifestations of any severe debilitating disease. I doubt the presence of any adrenal lesion. Although at one time there was in the serum a high value for potassium and a low value for sodium, the subsequent course of the disease was not particularly suggestive of adrenal insufficiency.

A PHYSICIAN: What do you think was the cause of the sudden rise in temperature and fall in blood pressure on the day before she died?

DR. LEVER: I think that may occur as a terminal event in almost any patient. She had bronchopneumonia, I suppose.

DR. R. H. FENNELL: Dr. Ford, would you tell us the impression on the ward?

DR. A. B. FORD: Our clinical impression was the same as Dr. Lever's. The diagnosis was not clear at first, but it gradually became more evident as the muscle weakness increased. Toward the end of her life the rash waxed and waned, the skin became taut and pigmentation was marked, particularly on the arms. The final event seemed to be an overwhelming infection. She had had numerous bouts of bronchopneumonia and was unable to tolerate them well.

CLINICAL DIAGNOSES

Dermatomyositis.
Bronchopneumonia.

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DR. LEVER'S DIAGNOSES

Dermatomyositis.
Bronchopneumonia.

ANATOMICAL DIAGNOSES

Dermatomyositis.
Pulmonary embolism, with infarction.

PATHOLOGICAL DISCUSSION

DR. FENNELL: At the post-mortem examination the body showed fairly generalized brownish pigmentation. There were a few abrasive lesions of the skin of the forehead and the back. Muscle

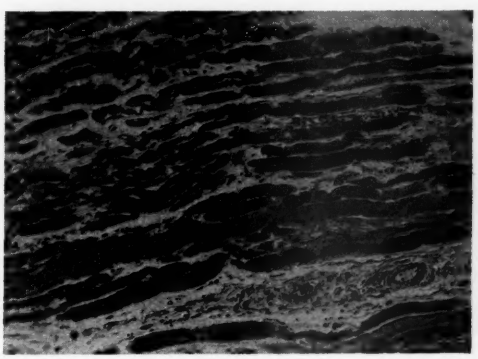

FIGURE 1.

atrophy was not marked, although it was present to a mild degree in some skeletal muscles. Microscopically the muscles showed marked changes. In a section from a pectoralis muscle (Fig. 1) the muscle fibers were wavy and varied in size. Some were hyalinized, with indistinctness or disappearance of cross striations. Stages in disintegration of muscle fibers from vacuolation to disappearance of the fiber were evident. In some of the sarcolemmal sheaths, as well as scattered elsewhere, were inflammatory cells. Plasma cells predominated,

although mononuclear cells and a few lymphocytes were seen. Neutrophilic leukocytes were infrequent. Clusters of pale nuclei in a syncytial mass were thought to be proliferation of sarcolemma cells. This destruction of muscle was seen in all the skeletal muscles examined and in the tongue and diaphragm. In the upper esophagus, involving the striated muscle only, there were a few damaged fibers and some inflammatory cell infiltrate. The remainder of the gastrointestinal tract was normal. The heart muscle was not involved. In the skin the epidermis was atrophied and the rete pegs were flattened. In the stratum Malpighii there was hydropic degeneration, and there was mild edema of the upper corium. A few inflammatory cells, plasma cells and monocytes, were present about the skin appendages and vessels. In one section the corium was thickened with dense collagen, and the sweat glands were in the center instead of the base of the corium. The blood vessels showed no changes. About some peripheral nerves were scattered lymphocytes.

Two infarcts were present in the lung; one about 4 cm. in diameter was at the left apex and a slightly smaller one was in the upper portion of the right lower lobe. Both were deep red and circumscribed and were of one to two weeks' duration. A yellow adherent embolus filled the branch of the pulmonary artery to the left upper lobe. In addition, small, partially organized yellow emboli were present in many tertiary branches of both pulmonary arteries. Thrombi in both femoral veins were yellow and partially organized; they were considered the source for the pulmonary emboli.

The liver was of approximately twice normal size and was yellow and greasy. Histologic study showed Sudan-positive vacuoles filling almost every cell, a few cells about the portal areas being spared. There was no fibrosis and no architectural change. I am unable to explain this marked fatty change except on the basis of malnutrition; I suppose that the dysphagia and sore mouth were factors in altering her diet.

The kidneys, pelvic organs, endocrine glands and brain showed no pertinent changes.

CASE 38152

Presentation of Case

A forty-eight-year-old Latvian was admitted to the hospital because of swelling of the abdomen.

Eleven years before admission the patient's way of life was disrupted by World War II. For the next six years, first under the German Occupation and then the Russian Occupation, his diet was grossly deficient, and at times he had nothing to eat for several days. Since then he had had postprandial heartburn, belching, constipation and epigastric distress; these were intermittent and never debilitating. There had been no jaundice, chills, fever or change in the color of the urine; the stools were occasionally clay-colored. Ten months prior to admission he noted a rather severe exacerbation of the postprandial epigastric distress, accompanied by nausea and some vomiting. The stools were normal in color, hard and at times flecked on the surface with bright-red blood. He was admitted to another hospital, where a gastrointestinal series allegedly revealed a duodenal ulcer; treatment with an ulcer diet and belladonna failed to relieve the symptoms. Three months before admission, when he vomited bright-red blood and later passed a tarry stool, he was admitted to another hospital; a gastrointestinal series again showed a duodenal ulcer. After nine blood transfusions, an exploratory laparotomy was performed; a nodular liver but no duodenal ulcer was found. Following the operation he felt fairly well until six weeks prior to admission, when he developed slowly progressive swelling of the abdomen that by two weeks prior to entry had progressed sufficiently to interfere with respirations. Three liters of fluid was removed by paracentesis, and the wound had drained profusely from then on. He had moderate dyspnea and nocturia (2 times). He had no relief of the epigastric distress on a soft diet without other medication. About six months prior to admission he noted the appearance of small yellow nodules around the eyes.

Physical examination showed a well developed, well nourished man who was moderately jaundiced. The heart and lungs were normal. There was tenderness in the epigastrium. A large, firm nodule could be palpated on the liver, which did not otherwise appear to be enlarged. The spleen was not palpable. A fluid wave and shifting dullness of the abdomen could be demonstrated. There was no peripheral edema.

The temperature was 98.6°F., the pulse 80 and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

The urine had a specific gravity of 1.016 and gave a + reaction for albumin and bile; the sediment contained 30 red cells per high-power field. Examination of the blood revealed a hemoglobin of 12.4 gm. and a white-cell count of 6100, with 51 per cent neutrophils and 36 per cent lymphocytes. The calcium was 9.8 mg., the phosphorus 3.9 mg., the nonprotein nitrogen 23 mg., the total protein 6.18 gm., the albumin 2.44 gm., the globulin 3.74 gm., the alkaline phosphatase 6.6 units, the total cholesterol 347 mg., with 87 per cent esters, and the bilirubin 2.0 mg. direct and 3.4 mg. total per 100 cc. The prothrombin time was 28 seconds (normal, 14 seconds), and a cephalin-flocculation test was ++ in twenty-four hours and +++ in forty-eight hours. A blood Hinton test was negative. The stools were guaiac negative. The ascitic fluid removed by paracentesis had a specific gravity of 1.010 and contained 4000 red cells and 740 white

cells (almost all lymphocytes) per cu. mm. and 1.6 mg. per 100 cc. of protein, of which 1 mg. was albumin; a cytologic smear was negative. A chest roentgenogram was negative. A gastrointestinal series showed moderate-sized varices and a small esophageal diverticulum in the lower esophagus; the liver was somewhat enlarged and the stomach was displaced to the left; no duodenal ulcer was seen.

He was treated with a low-roughage, low-sodium, high-protein diet, Mercuhydrin, intravenous albumin, Hykinone and ammonium chloride. Throughout his hospital stay he ate very poorly. The abdominal fluid rapidly reaccumulated, requiring a number of paracenteses for relief — up to 2400 cc. of fluid was removed. The jaundice remained unchanged. He developed a dull ache in the left upper quadrant that was unaffected by everything except lying on the right side, which gave him some relief. He had no nausea, vomiting, diarrhea or fever, and the physical examination remained unchanged.

On the nineteenth day an operation was performed.

Differential Diagnosis

Dr. John Homans, Jr.*: The beginning of this patient's story is of significance in that he had six years of a grossly deficient diet. His food, what there was of it, must have consisted largely of carbohydrates and must have been deficient in protein and vitamins. There is no mention of possible toxic substances. Cirrhosis of the liver may have multiple causes, but deficient diet is probably one of them. Following the period of starvation, he developed what may well have been symptoms of a duodenal ulcer, later demonstrated by x-ray examination. It is possible that disease of the liver may have contributed to these symptoms.

Ten months prior to admission he had an exacerbation of the "ulcer" symptoms, with x-ray demonstration of a duodenal ulcer. I do not believe that the failure of treatment, as described, without added detail as to how well or long this treatment was followed, would rule out duodenal ulcer.

Three months before entry he bled. With the subsequent demonstration of varices and lowered prothrombin activity and the two demonstrations of an ulcer, I do not see how one can tell from which he bled, nor do I believe it makes much difference in the final diagnosis. The failure to find the ulcer by x-ray examination is not definitive, especially if it was delayed for several days, although it should rule out malignancy.

Now I come to the development of signs, symptoms and laboratory findings, backed up by the observations at the laparotomy and by the x-ray examination, of intrinsic disease of the liver. The patient developed ascites, with consequent dyspnea and xanthelasma, possibly related to the high blood-cholesterol level. Physical examination showed jaundice, abdominal fluid and the important nodule on the liver. The urinalysis was remarkable only for the 30 red cells per high-power field, which might be due to a diseased prostate. If it did represent bleeding from cancer of the urinary tract, it was the only evidence of it. The blood counts were not remarkable, but they would rule out active infection. The reversed albumin-globulin ratio, slightly elevated phosphatase, decreased prothrombin activity and the positive cephalin-flocculation test all point to intrinsic disease of the liver. The high blood cholesterol with a high ester ratio would be more in favor of obstructive jaundice, but if one can make a decision from such tests, the weight of evidence is for intrinsic liver disease. The ascitic fluid is consistent with the diagnosis of cirrhosis. The gastrointestinal series indicated the presence of varices. Treatment aimed at avoiding difficulty with the varices and improving the liver status failed to improve the patient. I presume that the operation was to ascertain the nature of the nodule.

I shall make, then, a diagnosis of cirrhosis of the liver. I presume that it was Laennec's cirrhosis, for there was no evidence of a directly toxic or postinfectious etiology. The late development of jaundice and the failure to note the typical appearance should rule out biliary cirrhosis. I have also a probable diagnosis of duodenal ulcer, although I do not think that is important. The nodule that was felt on physical examination must have represented something that had grown since the laparotomy three months before admission. It seems unlikely that it represented a large regenerating nodule of liver tissue in a post-toxic or infectious hepatitis. A large nodule of a syphilitic liver can be ruled out by the appearance at laparotomy and by the negative blood Hinton test. There was no evidence in the history that suggested the possibility of an abscess, either pyogenic or amebic. There was no evidence to suggest the possible development of an echinococcus cyst. I presume that the nodule was not a distended gall bladder or cancer of the gall bladder.

I believe the most likely explanation for the nodule of the liver was a cancer, either metastatic or primary. If metastatic, from what? For the gastrointestinal tract I have only the fragmentary evidence of blood on the stools, although there were negative guaiac tests later; for the genitourinary tract, only the red cells in the urinary sediment. I cannot see that there was anything to suggest involvement of other organs. The most likely explanation, therefore, seems to me to be a primary carcinoma of the liver, developing, as it commonly does, on the basis of cirrhosis. One might expect to see fever and a greatly elevated phosphatase, instead of the slightly elevated one that he had, as confirmatory evidence, although I do not believe these are necessary. Certainly the possibility of

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this being an early superficial tumor of the liver would warrant exploration for possible removal.

In summary, I believe that this man developed cirrhosis of the liver, possibly on the basis of a long period of starvation, that he also had a duodenal ulcer and that he developed carcinoma of the liver, which would explain the nodule felt on the final admission.

Clinical Diagnoses

Hepatoma.
Portal cirrhosis, with esophageal varices.

Dr. Homans' Diagnoses

Carcinoma of the liver developing on cirrhosis.
Duodenal ulcer.

Anatomical Diagnoses

Hepatoma, with invasion of portal vein and metastases to lungs.
Cirrhosis.
Esophageal varices.

Pathological Discussion

Dr. David Kahn: At the original operation, performed three months before admission, the surgeon found a grossly nodular liver, which he suspected was cancerous. The biopsy of the liver at that time was most interesting, and there were certain equivocal features. The majority of the biopsy specimen was made up of segmented lobules of liver of varying sizes, but at the edge of these and scattered throughout the intervening fibrous septa were clumps and groups of larger, more eosinophilic liver cells, with small dark nuclei that lacked the nucleolus of the other liver cells and occasionally were binucleate. These cells did not definitely form the sinusoidal pattern of regenerating liver, and they lacked definite signs of malignancy, such as definite atypia or mitoses. In addition, there was degeneration of some of the liver cells, with parenchymatous fatty vacuolization of whole small lobules. The consensus of several pathologists was that this represented a very active stage of portal cirrhosis, with degeneration and marked regeneration, but that hepatoma could not be definitely excluded. This biopsy specimen was similar to a liver we had recently seen in a young boy who died of cholemia after two years of chronic or persistent low-grade hepatitis.

On admission here, in view of the original biopsy and the palpable nodule in the liver, it was believed that cancer should be definitely ruled out before rational therapy was outlined. As soon as the patient's condition warranted it, a liver biopsy was carried out under local anesthesia. At operation a large smooth nodule in the left lobe presented through the incision, and this was biopsied; in addition a needle biopsy was taken from another part of the liver. Whereas the latter resembled the first biopsy, the biopsy from the nodule in no way resembled it. This showed unequivocal hepatoma; there was very little recognizable liver tissue, but there were thick bands of fibrous tissue infiltrated by and surrounding large clumps of solid masses of poorly differentiated epithelial cells containing many mitoses and arranged in some areas in papillary fashion. Following the operation the patient's condition gradually deteriorated, and he died on the thirteenth postoperative day.

At autopsy the liver weighed 1620 gm. and was coarsely nodular throughout, with 0.3- to 0.5-cm. yellowish-brown nodules separated by bands of grayish fibrous tissue. A large single nodule measuring 4.5 by 3.5 cm. was in the left lobe, but grossly this was no different from the other nodules. Tissue of a similar nature, however, was found in radicles of the main portal vein. Histologically, hepatoma was found in sections from the large nodule, from the adjacent tissue around the hilum and in the portal vein and its branches, but only focally and occasionally in sections from other parts of the liver. Most of the liver showed the picture noted in the first biopsy, namely, advanced portal cirrhosis with very active regeneration and some areas of degeneration with parenchymatous fatty vacuolization. In addition, areas with intact lobular pattern were found in some sections, indicating that this was a postnecrotic or toxic variety of cirrhosis. There were a small metastasis to the lung, esophageal varices and ascites. The spleen was only slightly enlarged, weighing 200 gm., but there was definite fibrosis of the walls of the sinuses, suggesting long-standing congestion. There was no duodenal ulcer.

We were not able to make a definite statement about the connection between the period of severe malnutrition in this man and the subsequent cirrhosis. The occurrence of postnecrotic cirrhosis in human beings in whom there was no antecedent history of infection of the liver or poisoning (neither of which was present in this patient) has inclined many physicians to believe that nutritional deficiency may be a factor in the causation of this type of cirrhosis.

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FOOD FOR THE AGED

Aging is a mysterious process. Observed in all living things, it is yet little understood. In man, the most constant and evident sign is progressive loss of muscle power. Cerebration and cardiorespiratory, digestive and renal functions commonly have sufficient reserve to support such activity as remains possible. Much of senile deterioration has been attributed to arteriosclerosis, but this cannot satisfactorily explain aging until we know the nature of this disease. The influence of the food he eats on the aging of man is as yet unestablished.

A few old persons are overweight and continue to derive pleasure from food. Others lose weight and appetite and adopt diets, — by convenience, accident or poverty, — that may be poorly balanced or deficient; sometimes these diets are evident causes of poor health. In still others the diet may seem meager, but no ill effects are apparent and the subject can hardly be persuaded to make changes. One is reminded of the article written many years ago by the late Dr. Alfred Worcester denouncing the cruelty of trying to force old persons to eat more than they wish or are able to. By and large, the precision with which the food intake is adjusted to requirements is remarkable. The rarity of obese persons past sixty-five years of age is a grim reminder of the wages of dietary overindulgence.

There is little doubt that food preferences and idiosyncrasies of appetite become more marked with age. This development inevitably clashes with the dietary regimentation and mass production of institutional kitchens. A significant problem of institutions for the aged is a resolution of this conflict between kitchen methods and the appetite of aged persons.

The other consideration relating to these flagging appetites is that of nutritional adequacy. For example, the old man may prefer a constant diet of baked beans, but some means of securing the dietary essentials missing in baked beans must be found. One of Boston's most distinctive medical exhibits is a man who has on seven successive occasions in as many years been hospitalized with scurvy due to an exclusive diet of baked beans. For such a dilemma even more than a little codfish is required; a variety of natural foods, not vitamin pills or commercial concentrates, is to be preferred.

There is little evidence to suggest that the aged require more or less of the essential nutrients than do young adults. A diet styled and served to their particular tastes but with insistence on the "basic seven" is the goal.

The diets of these ancients should be looked to, perhaps, not only to find the faults therein but also to find in them the reason for survival.

GERMAN MEDICAL INTERNS IN THE UNITED STATES

Twenty-eight young German physicians are now spending sixteen-month internships in New Jersey community hospitals. Each of these physicians has been approved by the dean of his medical school

or the rector of his university and has been cleared by the High Commissioner of Germany. Each has also been guaranteed an important position on the teaching staff of his medical school or hospital when he returns. To each has been paid the regular hospital-intern stipend, supplemented by donations from various individuals and groups, from which the cost of his passage has been deducted. These arrangements were made after consultation with the hospitals, the State Department and the medical schools in Germany — but entirely outside the Government. A private agency was established, with the support of many individuals, to administer the plan, which is now working successfully. Occasional week-end professional-social visits to a large city have been arranged; these provide for visiting hospitals and museums, concerts and so forth and contacts with many types of Americans. A recent meeting in Atlantic City, called the "Forum on the Dynamics of Democracy," was designed to promote better international understanding. Instead of the usual presentation of clinical and scientific papers, many discussions were held; their topics ranged from civil rights to collective bargaining and industrial self-government. Many industrialists and jurists as well as eminent physicians attended.

This experiment is a farsighted one. These young men and women will take back to their country much of value, not only in medicine but in everyday life in these United States. In the past many of our older physicians and other scientists obtained much help and encouragement from the German medical schools and hospitals; today, in view of our world leadership in medicine, it is important that we share with other countries not only our medical knowledge but our experience with democracy.

DE VILLIERS FOUNDATION

On January 24 the *Journal* published the announcement of a prize to be awarded by the Robert Roesler de Villiers Foundation, Incorporated, for the most important paper submitted that makes any "significant contribution to the knowledge of the nature, causes, origin, treatment or cure of acute leukemia and allied diseases."

There is obviously a story behind such a foundation and such an offer. In this case it is that of an only child, a youth of exceptional promise and of exceptional advantages, who succumbed during the final year of his secondary-school education to one of those diseases whose mystery is still unsolved. It is the story of the desire, in the name and in the memory of this boy who would now be in his early manhood, had he lived, to try to find the hidden source of at least this one of the tragic instruments of death.

The establishment of such a foundation is by no means a new idea in this country, but it is one that gives added strength to a belief in our democratic institutions and to our faith in private enterprise. For aside from the great philanthropic endowments are many smaller ones of varying degrees of usefulness.

The modest memorial to Dr. Robert N. Nye, which was established to underwrite a particular task and which brought it to completion, was one. The small sum that had been thriftily set aside a few years ago for the education of a grandchild and was given, on his premature death, for an investigation of influenzal meningitis was another; from its employment came the first promising methods of treatment of that disease.

Care should be taken, however, that such private philanthropies are properly set up and intelligently administered, and not unduly restricted in their aims. If research is not confined to too narrow a path or too small an area, discoveries of true value will surely come to light. In view of these unquestioned facts, the open-hearted donors that our country still possesses must be taught to see the study of disease as a whole, and should be encouraged to join with others in the co-operative efforts that scientific investigation requires. More gold is recovered in the washing of many tons of gravel than in the search for isolated nuggets; it is the small gleams that must be followed.

The parents of Robert de Villiers, turning their grief into unselfish channels, have put themselves at the service of mankind. They are now trying to do unto others that which could not be done unto them, and medical science must help them toward their goal.

THE ANCIENT SACRIFICE

TIME has already erased from immediate consideration that solemn event — the passing of a king — that so deeply stirred Great Britain and the British Commonwealth and the people of their friends among the nations. A king is dead, but a benevolent monarchy lives on.

One of the most effective descriptions of the funeral pageantry and one of the most touching tributes to the late King himself was published in a medical journal, from the hand of a physician. As it appeared in the *Lancet* of February 23:

Kingship is a symbol made by man but greater than men, so that both King and subject are alike subject to it, and from the monarch it exacts a submission greater than any he requires from his people. The ancients might have called it fate, but fate is too external and mechanical a compulsion. It was the virtue of George VI that he accepted willingly and fully the obligation laid upon him, and by simply doing his duty he became great. To be born great, to have greatness thrust upon one, and then to achieve greatness is a conjunction Shakespeare can hardly have contemplated. And if the price was to work without ceasing, to subordinate even human relationships to the claims of duty, and to be lonely yet never to be left alone, it was a price paid gladly. It is not for the subject to pity his Sovereign, but to accept the sacrifice with pride and humility, and to see in it an example for his own life.

The man who dared to speak freely of the defective organization of the American Medical Association, has delivered a discourse before the Philadelphia County Medical Society, that sparkles with bright thoughts and wise suggestions.

Boston M. & S. J., *April 14, 1852*

MASSACHUSETTS MEDICAL SOCIETY

POSTGRADUATE LECTURE COURSE

John Ware Hall
Boston Medical Library
8 Fenway, Boston

Monday, April 14. *7:00–9:00 p.m.* PANEL DISCUSSION ON PERIPHERAL VASCULAR DISEASES. Chairmen: Drs. Edward A. Edwards and Joseph R. Stanton.
Discussers: Drs. Robert Linton, Theodore C. Pratt, Robert Wilkins, Edward A. Edwards and Joseph R. Stanton.

Wednesday, April 16. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30 p.m. **Practical Methods for the Evaluation of Pulmonary Function.** Dr. Edward A. Gaensler.

4:30–5:00 p.m. **The Significance of Hemoptysis.** Dr. Carlton R. Souders.

5:00–5:30 p.m. **Hidden Bronchiectasis in the Asthmatic Patient.** Dr. James H. Walker.

5:30–6:00 p.m. **The Value of the Boston Chest X-Ray Survey.** Dr. John H. Cauley.

Wednesday, April 23. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30 p.m. **The Management of Esophageal Lesions.** Dr. Herbert D. Adams.

4:30–5:00 p.m. **Modern Aspects of the Surgical Treatment of Tuberculosis.** Dr. John W. Strieder.

5:00–5:30 p.m. **An Evaluation of X-Ray Therapy for Intrathoracic Lesions.** Dr. Laurence L. Robbins.

5:30–6:30 p.m. **The Cancer Potential of Silent Pulmonary Shadows.** Dr. Richard H. Overholt.

TREASURER'S REPORT

COVERING REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to the district societies for 1952.

The Finance Committee voted to distribute the sum of $4000 to the district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 4563. Therefore, the refund to the district societies for each paid fellow is $0.877.

The following table gives the number of payments, as of March 1, and the refund to each district as of March 25.

DISTRICT	NO. REPORTED PAID	REFUND
Barnstable	39	$34.20
Berkshire	124	108.75
Bristol North	71	62.27
Bristol South	192	168.38
Essex North	170	149.09
Essex South	246	215.64
Franklin	40	35.08
Hampden	325	285.02
Hampshire	64	56.13
Middlesex East	161	141.19
Middlesex North	121	106.11
Middlesex South	832	729.11
Middlesex West	91	79.81
Norfolk	803	703.78
Norfolk South	146	128.04
Plymouth	138	121.02
Suffolk	578	506.55
Worcester	334	292.66
Worcester North	88	77.17
	4563	$4000.00

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DEATHS

GINGRAS — Albert F. Gingras, M.D., of Medford, died on March 26. He was in his forty-fourth year.

Dr. Gingras received his degree from Tufts College Medical School in 1933. He was a member of the New England Obstetrical and Gynecological Society and St. Luke's Guild of Catholic Physicians.

His widow and two children survive.

RONDEAU — Leo G. Rondeau, M.D., of Brighton, died on March 19. He was in his fifty-ninth year.

Dr. Rondeau received his degree from Tufts College Medical School in 1920. He was a fellow of the American Medical Association.

His widow survives.

CORRESPONDENCE

PHYSICIANS' RESPONSE TO CIVIL DEFENSE

To the Editor: The physicians and hospital administrators of Boston are to be complimented on their willing co-operation in the essential program of civil defense. The assistance of physicians in the Medical and Health Division of civil defense is indispensable, not only in organization but in participation in the event of an emergency, and it is with pleasure that I am able to report that the majority of physicians, residing or practicing in greater Boston, have responded wholeheartedly in setting up the program of this division. Over 800 physicians of Boston have already indicated their availability in the event of a disaster.

During the recent air-raid alert test held on February 21, 10:10 to 10:25 a.m., many doctors came to the various health units throughout the city or telephoned to obtain instructions. Over 100 reported in person to the health units at the onset of the first signal, the yellow alert. They were ready to care for persons seeking shelter and to supervise the following through of basic plans for emergency precautions and activity.

Five hundred and fourteen physicians reported by mail their location at the time of the alert so that in setting up plans for the future and in making assignments consideration might be given to the locality, hospital or emergency shelter that each doctor could reach most readily since the time element involved may mean the difference in the loss or saving of lives. It has been shown from the group reporting that the largest number of physicians practicing in Boston are in the Back Bay area at midmorning. Ninety-nine men indicated Back Bay as their location, whereas 61, the second largest group, reported that they were in Roxbury at the time of the test. The fewest available doctors were found in the outlying areas, such as Hyde Park, Roslindale, East Boston and West Roxbury; this indicates that the problems in organization for an actual disaster will be in locating physicians in suburban areas where most of the emergency hospitals will be set up.

The following tables showing location of physicians in midmorning might prove of interest.

Very truly yours,

JOHN H. CAULEY, M.D.
Chief Medical Officer
Boston Department of Civil Defense

Boston, Massachusetts

TOTAL NUMBER OF PHYSICIANS REPORTING BY LOCATION AT TIME OF ALERT

DISTRICT	ADDRESS	LOCATION
Allston-Brighton	23	28
Back Bay	279	99
Charlestown	7	9
Dorchester	30	29
Downtown Boston	15	34
East Boston	10	8
Hyde Park	6	4
Jamaica Plain	17	21
Mattapan	6	10
North End	6	10
Roslindale	3	6
Roxbury	46	61
South Boston	5	15
South End	28	38
West End	12	28
West Roxbury	9	9
Metropolitan Boston	12	60
Ill		3
Out of city		42
Totals	514	514
Total number of hospitals reporting		14
Total number of physicians reporting in person		112

RE MATCHING PLAN

To the Editor: In your issue of February 21 you had an editorial concerning itself with the new matching plan for the choosing of interns and criticizing the fact that certain hospitals had not kept faith with the promise, made to designated authorities, not to make commitments on their own. Being concerned as a father of one of the students involved, I have made numerous inquiries in this regard and should like to quote the following from a bulletin issued by the National Inter-Association Committee on Internships:

"A definite commitment by both the student and the hospital that each will rate the other 'one' is permissible under the matching plan, and if followed by both hospital and student assures appointment." I trust that you will make further inquiries into this matter, and I think that perhaps the national association responsible ought to make it clear to all students in this year's plan what their position was, in order that there may be no further misunderstanding.

BENJAMIN M. BERNSTEIN, M.D.

Brooklyn, New York

Note: Dr. Bernstein quotes correctly from the original communication of the National Inter-Association Committee on Internships, but the sentence following the one he quotes reads: "However, under no circumstances shall such prearrangements be a binding contract." Obviously this was ambiguous and somewhat contradictory. After the meeting of the students, the final description of the matching plan was announced in a pamphlet entitled "A Description of the Matching Plan for Internship Appointment," by F. J. Mullin and J. M. Stalnaker. On Page 2 of this pamphlet appears the following statement:

> . . . Under no circumstances, however, shall he (*the student*) enter into any binding contract, oral or written, with the hospital. Any 'promises' made by the hospital official or by the student prior to the announcement of the results of the matching plan shall have no force under this plan. The expression of choice through the official blanks sent in by the student and by the hospital is the only valid means of making the selections. Students and hospitals are specifically advised not to make promises or to ask for promises from each other.

Since the results of the internship-matching plan have already been announced, Dr. Bernstein's concern as a father of one of the students must have been adequately allayed. The students certainly fared better than did many of the best hospitals. — ED.

THE DOCTOR AND THE GOVERNMENT

To the Editor: I enjoyed the timely article on "The Relation of the Surgeon to His Government" by Dr. W. J. Mixter in a recent issue of the *Journal.* His statement that "We must not stand aloof, but we should do all in our power to lead in the proper development of our relations to the government in the future" indicated a sound policy that we all should think about.

There is no doubt that the increasing role of government in our daily lives is seen, and we are being asked constantly to play a more important role ourselves. In many communities the care of the aged is practically run like a government-sponsored bureau; all physicians who see these patients are easily reminded that the financial problem is solved by the government. The amount of care given these patients is rising yearly. Many problems are still arising, but in spite of these the most important thing is that the system exists and we should try to understand it and help to correct some of the medically unjust rules.

The increasing importance of the Veterans Administration in the years to come is a fact; for many of us, who are surgeons in areas where the bed shortage is a problem, it is a distinct advantage to be able to send a veteran to these hospitals. However, the big problem is the future years, when the number of veterans will be increasing and when the medical care of the family will probably soon be taken for granted. I believe that the societies should actually enter into the picture and probably guide the program so that, as Dr. Mixter says, the patient gets the best possible care.

The problem of service-connected disabilities or whether the veteran can afford care is only a point of discussion, because a careful check into the files of the Veterans Administration shows that this is not an item.

I am sure most of us who have been in World War II and have been trained for surgery today are willing to help humanity and to co-operate with the Government if it is within our power.

Thank you for a good article on an issue about which more will be heard.

S. ALBERT SARKISIAN, D.M.D., M.D.

Brockton, Massachusetts

NONCLINICAL NOTES

Dr. George P. Denny of Boston, a graduate of Harvard Medical School and a fellow of the Massachusetts Medical Society, has been appointed manager of the new 949-bed general medical and surgical Veterans Administration Hospital in Boston.

Dr. Denny has been since 1949 manager of the West Roxbury Veterans Administration Hospital.

Dr. Henry R. Viets, librarian of the Boston Medical Library, has been appointed Lecturer on Neurology and Historical and Cultural Medicine at the University of Texas Medical Branch at Galveston.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Prothrombin Deficiency. By Rosemary Biggs, M.D. Department of Pathology, Radcliffe Infirmary, Oxford. 8°, cloth, 83 pp. with 14 illustrations and 10 tables. Springfield, Ill.; Charles C Thomas, 1951. $2.50.

In this monograph Dr. Biggs discusses the estimation, measurement and one-stage and two-stage testing of prothrombin and an investigation of hypoprothrombinemia. Much of the material was included in Dr. Biggs' thesis for the degree of doctor of medicine, in the University of London.

The Public Health Nurse and Her Patient. By Ruth Gilbert, R.N., co-ordinator, Course for Mental Hygiene Consultants, and assistant professor of nursing education, Columbia University Teachers College. 8°, cloth, 348 pp. Cambridge, Massachusetts. Published for the Commonwealth Fund by the Harvard University Press, 1951. $3.75.

The first edition of this standard textbook was published in 1940. This edition has been revised and expanded to include new material in the field of mental hygiene. A bibliography of over 100 titles and a good index conclude the text. The book is well published and should be in all collections on public health and nursing.

Causalgia. By Frank H. Mayfield, M.D., assistant professor of clinical surgery, University of Cincinnati College of Medicine, and attending neurological surgeon, Bethesda Hospital, Christ Hospital, Deaconess Hospital, Good Samaritan Hospital, St. Francis Hospital and Jewish Hospital, Cincinnati, Ohio. 8°, cloth, 65 pp., with 12 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication No. 58, American Lecture Series.)

This monograph is devoted to a discussion of extreme nerve pain and its treatment, principally by sympathectomy.

Allergy in Relation to Pediatrics. By Bret Ratner, M.D., professor of clinical pediatrics (allergy) and associate professor of immunology, New York Medical College, attending pediatrician, Flower and Fifth Avenue Hospitals, and director of pediatrics, Sea View Hospital. 12°, cloth, 228 pp. Saint Paul, Minnesota: Bruce Publishing Company, 1951. $3.75.

This small volume contains the papers read by 17 specialists at a panel discussion held at the fifth annual meeting of the American College of Allergists, Chicago, 1949.

Space Medicine: The human factor in flights beyond the earth. Edited by John P. Marbarger, associate professor of physiology, College of Medicine, and director of research in the Aeromedical and Physical Environment Laboratory, University of Illinois. 8°, cloth, 83 pp., with 18 illustrations. Urbana, Illinois: University of Illinois Press, 1951. Cloth bound, $3.00; paper bound, $2.00.

In this small volume are presented six papers read at a symposium held in Chicago in 1950.

NOTICES

ANNOUNCEMENT

Dr. Isadore Kaplan announces the removal of his office to Holyoke Soldiers' Home Hospital, Holyoke, Massachusetts.

SOUTH END MEDICAL CLUB

The South End Medical Club will hold its annual hospital meeting at St. Elizabeth's Hospital, Brighton, on April 15 at 11:30 a.m. Dr. Cornelius J. Shea will discuss "Diverticulitis: Modern Management"; Dr. William J. Colpoys, "Problems in Diabetes"; Dr. Sylvester K. McGinn, "Pulmonary Embolism"; and Dr. John W. Spellman, "Unusual Cases of Malignant Disease."

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, April 16, at 8 p.m.

Dr. Arthur L. Watkins, chief of the Department of Physical Medicine at Massachusetts General Hospital and medical director of the Bay State Medical Rehabilitation Clinic, will speak on "Recent Experiences at the Bay State Medical Rehabilitation Clinic."

A general discussion will conclude the program.

Physicians, physical therapists, occupational therapists and students are invited to attend.

HARVARD MEDICAL SOCIETY

The Harvard Medical Society will meet on April 22 at 8 p.m. in the White Building Amphitheatre (Floor 3A) of the Massachusetts General Hospital. The program will be presented by the Department of Medicine of the hospital; Dr. Walter Bauer will preside.

Program

Some Hormonal Aspects of Water Excretion in Man — Dr. Alexander Leaf.

The Fate of Therapeutic Doses of I^{131} in Carcinoma of the Thyroid Gland — Dr. John B. Stanbury.

Studies of Cholesterol Synthesis In Vitro — Dr. Ivan D. Frantz, Jr.

Observations on the Mechanism of Action of Thyroxine — Dr. Charles H. DuToit.

Toxic Products of Proteolysis — Dr. Robert L. Berg.

Pathogenesis of Fungal Infections in Patients Treated with Antibiotics — Dr. Thomas F. Paine, Jr.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The New England Society of Anesthesiologists will present a program on "The Relation of Gynecology and Obstetrics to Anesthetic Agents" on May 3 as part of its Postgraduate Education Program.

Program

Respiration Before Birth and Its Significance in Anesthesiology — Dr. Franklin Snyder, Boston Lying-in Hospital.

Resuscitation of the Newborn as Related to Obstetrical Anesthesia — Dr. Clement A. Smith, Boston Lying-in Hospital.

Anesthesia in Geriatric Gynecology — Dr. John Schleicher, Hanover, New Hampshire.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The Massachusetts Society of Examining Physicians will hold its annual meeting at the Harvard Club, Boston, on May 7, at 6 p.m. Dinner will be served at 7, after which Samuel Sears, president of the Massachusetts Bar Association, will speak on "The Relation of the Practicing Attorney to the Examining Physician" and Eugene H. Giroux, chairman of the Massachusetts Industrial Accident Board, will discuss "The Practices of the Industrial Accident Board as They Affect the Examining Physician."

AMERICAN COLLEGE OF SURGEONS

A sectional meeting of the American College of Surgeons will be held May 15–17 in Toronto, Ontario.

On May 15 teaching clinics and demonstrations will be presented in Toronto hospitals. Scientific sessions will be held at the Royal York Hotel on May 16 and 17. Papers, panels and symposia on current surgical problems and new surgical motion pictures and a stereoscopic colored film on "Radical Resection for Carcinoma of the Stomach" will be presented.

Hotel accommodations may be obtained by writing to Mr. G. R. Street, Convention Manager, Royal York Hotel, Toronto, Ontario.

KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPAEDIC SURGERY

A prize of $1000, donated by the Kappa Delta Sorority, may be awarded annually by the American Academy of Orthopaedic Surgeons for the best research related to orthopedic surgery and carried out by an American citizen in the United States. This research must be presented to the Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons before November 1, 1952. Further information may be obtained from Dr. Claude N. Lambert, 104 South Michigan Avenue, Chicago 3, Illinois.

SOCIETY MEETINGS AND CONFERENCES

APRIL 10–15. Boston City Hospital House Officers' Association. Page 476, issue of March 20.

APRIL 12–30. Springfield Hospital. Page 433, issue of March 13.

APRIL 14–23. Postgraduate Lecture Course. Page 593.

APRIL 14–25. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

APRIL 15. South End Medical Club. Page 595.

APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

APRIL 16. New England Society of Physical Medicine. Page 595.

APRIL 16. Phi Chi Medical Fraternity — Delta Chapter (Tufts). Page 521, issue of March 27.

APRIL 17–19. Boston Lying-in Hospital and Children's Hospital. Postgraduate Course in Obstetrics and Pediatrics. Page 433, issue of March 13.

APRIL 21–25. American College of Physicians. Page 522, issue of March 27.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 22. Harvard Medical Society. Page 595.

APRIL 22. Norfolk District Medical Society. Page 710, issue of November 1.

APRIL 22, 25 AND 29. Boston City Hospital House Officers' Association. Page 559, issue of April 3.

APRIL 23. Massachusetts Academy of General Practice. Springfield. Page 560, issue of April 3.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

APRIL 25 AND 26. Texas Medical Center. Page 354, issue of February 28.

APRIL 26. Boston City Hospital Alumni Association. Page 476, issue of March 20.

APRIL 26. Alumni Association of Long Island College of Medicine. Page 434, issue of March 13.

MAY 3. New England Society of Anesthesiologists Postgraduate Education Course. Page 996, issue of December 20 and page 476, issue of March 20.

MAY 3. New England Society of Anesthesiologists. Page 595.

MAY 3. Boston University School of Medicine Alumni Association. Page 560, issue of April 3.

MAY 3. Annual Meeting. Massachusetts Association of Medical Technologists, Inc. Page 433, issue of March 13.

MAY 7. Massachusetts Society of Examining Physicians. Page 595.

MAY 8. The Choice of Patients for the Surgical Treatment of Hypertension. Dr. James A. Evans. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MAY 8–10. American Neurological Association. Page 559, issue of April 3.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 15–17. American College of Surgeons. Notice above.

MAY 19–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 21 AND 22. Venereal-Disease Seminar. Page 559, issue of April 3.

MAY 22–24. American Academy of Pediatrics. Page 522, issue of March 27.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Page 476, issue of March 20.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 19–21. American Association of Genito-Urinary Surgeons. Page 434, issue of March 13.

JUNE 22–26. American Society of Medical Technologists. Twentieth Annual Convention. Portland, Oregon.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–11. International Congress of Dietetics. Page 434, issue of March 13.

JULY 7–12. International Diabetes Federation. Page 316, issue of February 21.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

JULY 24–26. Conference on Aging. Page 559, issue of April 3.

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 522, issue of March 27.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 3–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

APRIL 30. Hotel Continental, Cambridge.

NORFOLK

APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 17

THURSDAY, APRIL 17

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
12:00 m.–1:00 p.m. Weekly guest speaker — Dr. Chester Howe. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Medical Division Lecture. Mount Auburn Hospital, Cambridge.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheatre, New England Deaconess Hospital.

FRIDAY, APRIL 18

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatrics. Woolson II, Mount Auburn Hospital, Cambridge.
*1:00–2:00 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
2:00–4:00 p.m. Arthritis Conference. Stearns Auditorium, New England Center Hospital.
4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

MONDAY, APRIL 21

8:30 a.m. Eye Clinical Conference. Massachusetts Eye and Ear Infirmary. Out Patient Department.
8:30–9:30 a.m. Surgical Clinic by entire staff. Cheever Amphitheatre, Dowling Building, Boston City Hospital.
*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.
12:00 m. Pediatric Medical-Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.

(Notices concluded on page xix)

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